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ABOUT COVER

Peer Review of *World Journal of Stem Cells*, Asmaa Mohammed Shamseldeen, MD, Assistant Professor, Department of Physiology, Cairo University, Cairo 30411, Egypt. asmaa82shamseldeen@gmail.com

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MINIREVIEWS

Current perspectives on mesenchymal stem cells as a potential therapeutic strategy for non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has emerged as a significant health challenge, characterized by its widespread prevalence, intricate natural progression and multifaceted pathogenesis. Although NAFLD initially presents as benign fat accumulation, it may progress to steatosis, non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma. Mesenchymal stem cells (MSCs) are recognized for their intrinsic self-renewal, superior biocompatibility, and minimal immunogenicity, positioning them as a therapeutic innovation for liver diseases. Therefore, this review aims to elucidate the potential roles of MSCs in alleviating the progression of NAFLD by alteration of underlying molecular pathways, including glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis. The insights are expected to provide further understanding of the potential of MSCs in NAFLD therapeutics, and support the

development of MSC-based therapy in the treatment of NAFLD.

Key Words: Non-alcoholic induced fatty liver disease; Mesenchymal stem cells; Lipid accumulation; Inflammation; Oxidative stress; Endoplasmic reticulum stress; Fibrosis

Core Tip: This review highlights the increasing incidence of non-alcoholic fatty liver disease and its complex progression, focusing on the underlying mechanisms of disease pathogenesis and contemporary treatment modalities. It delves into the therapeutic potential of mesenchymal stem cells, examining their classification, roles, and primary functions in the context of their use in various diseases. The review specifically aims to clarify how mesenchymal stem cells can mitigate non-alcoholic fatty liver disease progression by modulating molecular pathways involved in glycolipid metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and fibrosis.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease occurring globally. Recent research has shown that the prevalence of NAFLD over the past four decades is estimated to be around 30%, with varying rates across different regions such as 44% in Latin America and 28% in the Asia Pacific[1]. This increase in prevalence is closely linked to the rising trends of obesity, type 2 diabetes mellitus (T2DM), insulin resistance (IR), cardiovascular disease (CVD), and hypertension[2]. Over the last two decades, numerous clinical trials have investigated targets in the development of drugs for non-alcoholic steatohepatitis (NASH). However, owing to the disease's inherent heterogeneity and the intricate nature of its pathogenesis, few drugs have yet received approval for clinical intervention[3].

Mesenchymal stem cells (MSCs), commonly found in various tissues, exhibit intrinsic capabilities for high self-renewal, excellent biocompatibility, and low immunogenicity. These properties have positioned MSCs and their secretory factors as therapeutic innovations for various diseases[4]. Extensive research is currently being carried out to explore the potential of MSCs as a therapeutic approach to NAFLD. Preliminary studies have highlighted their potential efficacy in alleviating liver damage, improving liver function, and inducing liver regeneration[5]. This review aims to highlight and summarize the emerging therapeutic potential of MSCs in treating NAFLD, with a focus on elucidating the mechanisms that ameliorate the disease. For this review, articles published in English were searched on PubMed using the keywords "non-alcoholic fatty liver disease", "metabolic-associated fatty liver disease", "fatty liver", "non-alcoholic steatohepatitis", "mesenchymal stem cells", and "stem cells".

OVERVIEW OF NAFLD

The heterogeneous progression of NAFLD

NAFLD is characterized by its heterogeneity, as it includes a spectrum of liver diseases. This diversity in disease manifestations has positioned NAFLD as a major contributor to liver transplantation worldwide, primarily due to its progression to cirrhosis and hepatocellular carcinoma (HCC)[6]. Previous studies indicate that patients with NAFLD have a greater risk of all-cause mortality than the general population, including increased risks for extrahepatic diseases such as CVD, chronic kidney disease, and certain cancers[6]. Notably, close relatives of individuals with NAFLD-induced cirrhosis face a 12-fold increase in the risk of developing advanced fibrosis, which can be attributed to genetic factors[7].

NAFLD typically progresses through stages that include steatosis, fibrosis, cirrhosis, and eventually HCC. However, the progression of the disease is unpredictable, with variable shifts in disease severity and the stages of fibrosis. Assessing liver tissue damage involves monitoring the fibrosis status and detecting the onset of cirrhosis, which are critical for understanding the development of this disease. A 4-year study involving 1773 adults with NAFLD demonstrated that increasing mortality rates are correlated with increased fibrosis severity, with stages F3 and F4 also associated with an increased chance of liver complications, T2DM, and reduced kidney function[8]. NAFLD progresses rapidly in patients with NASH, which further increases the risk of HCC and associated morbidities[6]. In contrast, NAFLD patients without cirrhosis exhibit a significantly lower incidence of HCC[9].

Mechanisms underlying NAFLD pathogenesis: A quick glance

The intricate mechanisms underlying the onset and progression of NAFLD remain elusive. Historically, the pathogenesis of NAFLD can be explained by the two-hit hypothesis. The first hit, marking disease initiation, involves lipid accumulation and IR. These imbalances promote hepatic lipogenesis and reduce the degradation of free fatty acids, leading to hepatic steatosis[10]. The subsequent stage, or the second hit, increases the susceptibility of the liver to inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress. During this phase, the resulting increase in mitochondrial reactive oxygen species (ROS) can trigger inflammation (steatohepatitis), fibrosis, and lead to cirrhosis[10]. However, as research has progressed, this two-hit hypothesis seems insufficient to fully capture the complexity of NAFLD pathogenesis.

An improved understanding of the pathogenic mechanisms in NAFLD has led to the emergence of a multiple-hit hypothesis. This hypothesis posits that the disease results from various intertwined factors, encompassing genetic, environmental, and microbiological elements, and affects multiple organs, including the liver, pancreas, gut, and adipose tissue[11]. In the initial phase of the disease, IR and obesity are considered foundational triggers that lead to fat accumulation and liver lipotoxicity. Subsequent contributors to NAFLD progression include elevated levels of free fatty acids and triglycerides, which trigger the disease from mere steatosis to more complex stages[12]. Other contributing factors include oxidative stress, liver-derived inflammatory mediators (cytokines from Kupffer cells), and agents from external sources such as adipokines and lipopolysaccharides originating from the gut microbiota. Collectively, these factors lead to hepatocellular injury, apoptosis, compensatory hepatocyte regeneration, liver fibrosis, and NAFLD progression[11,12].

Current treatment approaches for NAFLD

At present, no pharmacological treatments have been officially approved for NAFLD, despite an extensive understanding of its epidemiology, pathogenesis, and progression. Generally, interventions include lifestyle changes such as a hypocaloric diet and physical exercise, as well as weight loss induced by drugs or bariatric surgery.

Diet modification plays a critical role in NAFLD management. Diets highly recommended for NAFLD patients include hypocaloric diets, high-protein diets, and the Mediterranean diet. Particularly, the Mediterranean diet is frequently advocated as it contains a rich source of bioactive compounds and phytochemicals, such as omega-3 fatty acids and phytosterols, known for their antioxidant and anti-inflammatory benefits[13].

In addition to dietary changes, exercise has shown positive effects on NAFLD outcomes in animal models by altering liver metabolism. This alteration involves the regulation of SREBP-1 levels through AMPK activation, which potentially increases peroxisome proliferator-activated receptor (PPAR)-γ expression. Additional benefits observed from regular exercise include improved insulin sensitivity, reduced oxidative stress, and mitigated hepatocyte apoptosis through the upregulation of antioxidative enzymes and anti-inflammatory cytokines[14]. However, studies on NAFLD patients are relatively limited in terms of exercise type, duration, and intensity[15].

Weight loss achieved through these dietary and exercise interventions has been demonstrated to improve NAFLD outcomes, including enhanced glucose control, which subsequently reduces the risks of diabetes and CVD[15]. Specifically, in patients with NASH, weight reductions of up to 10% have been associated with decreased hepatic steatosis and fibrosis regression[16]. Additionally, biopsy-confirmed NASH patients have pharmacological treatment options, which include vitamin E and pioglitazone. Vitamin E, acting as an antioxidant, neutralizes free radicals and reduces oxidative stress. Treating NASH patients with 800 IU/day of vitamin E has been shown to improve liver histology compared to a placebo[17]. However, vitamin E can cause side effects such as bleeding, heart failure, and prostate cancer; therefore, its long-term high-dose usage should be evaluated against international guidelines. Pioglitazone is used to treat NASH in both diabetic and non-diabetic patients. Both groups have shown improvements in fibrosis scores, insulin sensitivity, and significant reductions in hepatic triglyceride content[18]. However, its use comes with potential side effects, including increased risks of certain cancers such as bladder cancer, weight gain, fluid retention, and cardiovascular events. Other alternatives to improve NAFLD/NASH outcomes include bariatric surgery and liver transplantation. However, extensive clinical trials are required for more conclusive results before these can be implemented as a standard course of treatment.

THERAPEUTIC POTENTIAL OF MSCs

Classification and characterization of MSCs

MSCs are multipotent stem cells that are derived from a diverse array of stromal regenerative cells obtained from various tissues. These sources include bone marrow, adipose tissues, umbilical cord, dental pulp, menstrual blood, synovium, amniotic fluid, and placenta. The International Mesenchymal and Tissue Stem Cell Committee has proposed specific criteria for the identification of human MSCs. Specifically, MSCs should adhere to plastic under standard conditions. Furthermore, flow cytometry analysis should reveal that these cells express the CD markers CD105, CD73, and CD90, and not express CD45, CD34, CD14 or CD11b, CD79a, CD19, or HLA-DR. Additionally, these cells should demonstrate the ability to differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro*[19].

The multifaceted roles and primary functions of MSCs

MSCs have become a vital component of regenerative medicine due to their inherent self-renewal capability and ability to differentiate into various cell lineages. Additionally, MSCs secrete many factors that play pivotal roles in preserving tissue equilibrium, aiding in repair, and promoting regeneration[20]. The complex process of wound healing, involving

cell migration, proliferation, matrix remodeling, angiogenesis, and re-epithelialization, is significantly improved by MSC intervention. MSCs accelerate healing by promoting angiogenesis, cell proliferation, collagen production, inflammation moderation, and overall tissue regeneration through the release of various chemotactic agents[21,22].

MSCs also exert significant immunomodulatory effects *via* both the innate and adaptive immune systems. They establish direct interactions with numerous immune cells, such as T cells, B cells, natural killer cells, macrophages, monocytes, dendritic cells, and neutrophils, through cell-to-cell contact and paracrine signaling[23]. MSCs promote the secretion of anti-inflammatory mediators such as interleukin (IL)-10 and transforming growth factor-β while attenuating the secretion of proinflammatory cytokines, including IL-1 and IL-17. Additionally, MSCs secrete chemokines that attract immune cells, thus enhancing their immunosuppressive functions[24]. Recent studies have clarified the role of MSCs and their secretory factors in anti-inflammatory processes. Their mode of action relies on interactions with various cellular targets, such as macrophages, microglia, chondrocytes, endothelial cells, fibroblasts, and neural stem cells[25].

Due to their intrinsic trophic, immunomodulatory, and homing attributes, MSCs possess great therapeutic potential. Specifically, they have a natural ability to seek and settle in sites of tissue injury, inflammation, or tumors, thus providing them with a distinct advantage in targeted interventions through immunomodulation, bioactive secretion, and cellular differentiation. In line with these characteristics, MSCs have also been shown to serve as delivery systems to transport therapeutic agents, genes, or proteins directly to specific tissues or tumor sites[26].

Therapeutic potential: Exploiting MSCs for the treatment

The therapeutic potential of MSCs for various medical conditions has been demonstrated in numerous animal models and clinical trials. These conditions include organ injuries to the heart, liver, kidneys, and lungs, often resulting from trauma or cellular changes[27], as well as neurological disorders such as Alzheimer's disease, in which MSCs have replaced dying neurons and alleviated inflammation[28]. Additionally, MSCs are currently being studied for the treatment of stroke, Parkinson's disease, and Huntington's disease. MSCs have also shown capabilities in mitigating oxidative stress and providing protective effects against endocrine disorders such as diabetes[14]. Conditions such as thyroid irregularities, osteoporosis, adrenal insufficiency, and pituitary gland irregularities have also been ameliorated by MSC administration[29].

Numerous preclinical studies have highlighted the therapeutic potential of MSCs in alleviating lung injuries and fibrosis in respiratory conditions, including bronchopulmonary dysplasia, asthma, acute lung injuries, and chronic pulmonary diseases in adults[30]. MSCs have shown benefits for rheumatoid arthritis by reducing inflammation and decelerating its progression[31]. They also provide therapeutic benefits for conditions like systemic lupus erythematosus, multiple sclerosis, and Crohn's disease, as evidenced in both preclinical and clinical studies[32]. Research suggests that MSCs can differentiate into cardiomyocytes both *in vitro* and *in vivo*. This capability could potentially benefit patients with dilated cardiomyopathy by rejuvenating endothelial function and enhancing coronary circulation[15]. Furthermore, MSCs are being investigated for the treatment of other conditions, including fractures, infertility, and obesity. Nevertheless, challenges remain concerning the safety, efficacy, and long-term impacts of MSC treatments.

THE ROLES OF MSCs IN TREATING NAFLD/NASH

NAFLD/NASH is a leading cause of chronic liver disease, resulting in significant morbidity and mortality. Currently, NAFLD/NASH not only represents a mounting global concern but also signifies a considerable unmet medical need due to the lack of licensed drugs. MSCs are characterized by their rapid proliferation, minimal immunogenicity, and low tumorigenicity. Possessing self-renewal and multi-differentiation capabilities, they provide immunomodulatory and tissue repair functions, primarily through the secretion of trophic factors, cytokines, and chemokines[20]. Due to these beneficial biological characteristics, both MSCs and their derivatives emerge as promising cellular therapies for various diseases, including NAFLD/NASH (Figure 1).

MSCs improved glucose and lipid metabolism in NAFLD/NASH

Emerging evidence underscores the central role of liver IR and abnormalities in glucose and lipid metabolism in the pathophysiological features of NAFLD[10]. Various therapeutic measures have been explored to address these challenges. Among these, MSCs and their secretory factors are notable for their ability to mitigate the harmful effects of a high-fat diet on liver health, and address issues such as steatosis, liver dysfunction, and metabolic imbalances in NAFLD rat models and hepatocytes induced by palmitate[33-37]. Among specific types of MSCs, umbilical cord MSCs (UC-MSCs) have been recognized for their positive influence on lipid metabolism. This effect is achieved by their ability to upregulate the expression of genes associated with fatty acid oxidation and lipogenesis, consistent with the observed increased expression of protein in the HNF4α-CES2 pathway[38]. Additionally, exosomal miR-627-5p sourced from UC-MSCs promotes glucose and lipid metabolism, thereby alleviating liver damage in NAFLD. This protective mechanism operates by inhibiting the expression of obesity-associated genes[39]. On the other hand, transplantations involving adipose-derived stem cells (ADSCs) have shown promise in reversing pathological hepatic changes, reducing lipid accumulation, and restoring liver function in NAFLD models[40,41]. Concurrently, ADSC-derived extracellular vesicles (ADSC-EVs), which are rich in miR-223-3p, have been shown to suppress lipid accumulation by targeting the *E2F1* gene, suggesting a potential strategy for slowing NAFLD progression[42]. Hepatocyte growth factor derived from menstrual blood-derived stem cells actively downregulates Rnf186 expression, which in turn promotes an increase in hepatic glycogen storage and reduces lipid buildup in NAFLD. This process is mediated through the AMPK-mechanistic target of rapamycin pathway[43].

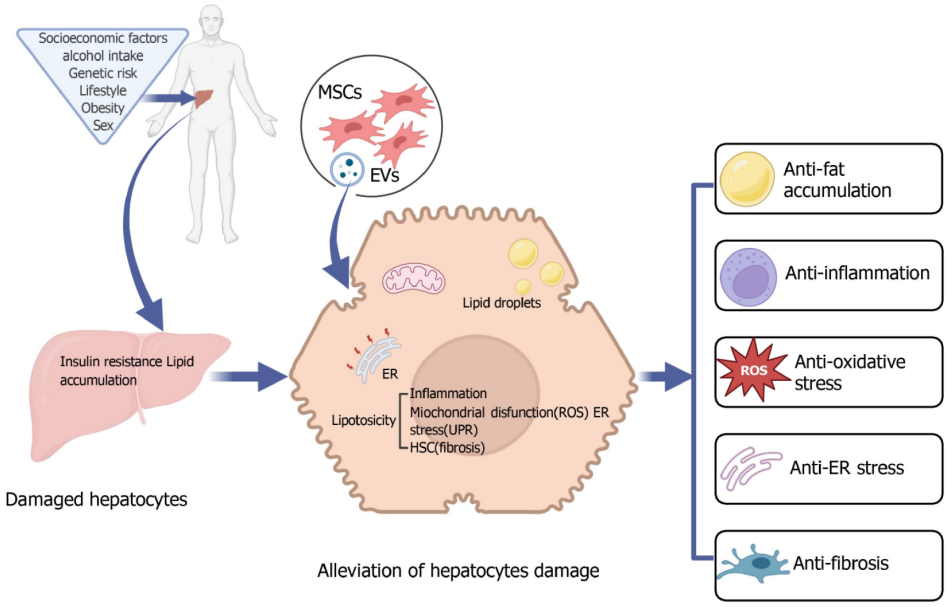

Figure 1 The therapeutic efficacy of mesenchymal stromal/stem cells and mesenchymal stromal/stem cell-derived secretory factors in managing non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Hepatic insulin resistance and lipid accumulation are exacerbated by multiple detrimental factors, resulting in hepatocyte damage. The transplantation of mesenchymal stem cells (MSCs) and their derived secretory factors introduces a holistic approach to liver health. These cells not only regulate lipid metabolism and enhance insulin sensitivity but also reduce fat accumulation in the liver. Their anti-inflammatory properties are emphasized by their ability to inhibit the activation of immune cells, such as Kupffer cells and natural killer cells, and by their role in reducing the secretion of pro-inflammatory cytokines. Additionally, MSCs produce antioxidants that neutralize reactive oxygen species in the liver, thereby mitigating both oxidative stress and endoplasmic reticulum stress. In countering liver fibrosis, MSCs play a prominent role by suppressing hepatic stellate cells, releasing anti-fibrotic factors, and aiding in hepatocytes repair. Moreover, these stem cells secrete cytokines that are crucial for liver tissue repair and regeneration. MSC: Mesenchymal stem cell; EVs: Extracellular vesicles; ER: Endoplasmic reticulum; ROS: Reactive oxygen species; HSC: Hepatic stellate cell.

With respect to NASH-focused research, investigations have shown notable decreases in hepatic lipid content following the administration of MSCs. An innovative method, in which mitochondria from human MSCs are transplanted into mouse hepatocytes with NASH, has been identified as a potential strategy to amplify lipid utilization by enhancing mitochondrial oxidative capacities, regardless of diverse pathogenic incidents[44,45]. Further exploration revealed that the Notch signaling pathway is instrumental in decreasing apoptosis in steatotic hepatocytes and promoting cellular proliferation in hepatocytes from NASH mice following ADSC treatment[46]. Concurrently, cotreatments involving bone marrow-derived MSCs (BMSCs) and BMSC exosomes (BMSC-Exos) led to marked reductions in hepatic steatosis and ballooning in NASH. Specifically, BMSC-Exos (120 μg/kg) displayed significant antisteatotic properties that are characterized by the downregulated expression of fatty acid synthesis genes (SREB1, 2 and ACC) and lipid uptake molecules (CD36), along with the upregulated expression of fatty acid oxidation genes (PPARα and CPT1)[47]. Another investigation highlighted that the fact that antioxidant-fortified MSCs diminished oxidative stress, subsequently reducing fat accumulation in the liver. This strategy has emerged as a potential remedy for conditions such as obesity and prediabetes and might alleviate complications such as NAFLD[48]. Conversely, a separate study presented evidence suggesting that treatments with either MSCs or MSCs-EVs did not significantly change fat accumulation in NASH, as assessed through histological analysis[49]. Despite the promise of MSCs and their secretions in the treatment of liver glucose and lipid imbalances in NAFLD/NASH, more research needs to be done to obtain consistent and reliable outcomes.

Anti-inflammatory effects of MSC therapy in NAFLD/NASH

Fat accumulation in the liver, which is characteristic of NAFLD/NASH, induces endoplasmic reticulum (ER) stress and oxidative stress, which in turn leads to increased lipid peroxidation and increased levels of ROS. This biochemical disturbance activates inflammatory pathways, prompting an immune response that attracts inflammatory cells to the liver. Once present, these cells release inflammatory cytokines, thereby intensifying liver inflammation and causing subsequent damage. Recent studies in NAFLD mice have illustrated the effectiveness of MSCs and MSC-Exos in significantly reducing inflammatory cell infiltration in liver lobules[33,37]. Similarly, the transplantation of ADSCs has shown profound benefits in NAFLD, notably reducing the expression levels of critical proinflammatory markers such as tumor necrosis factor (TNF)-α and IL-6[41]. Furthermore, MSCs and MSC-conditioned medium (MSC-CM) have demonstrated efficacy in neutralizing inflammation and cellular apoptosis in T2DM/NAFLD, with the protective effect attributed to the Sirt1 protein[36,50]. Additionally, stem cell transplantation results in decreased plasma inflammatory cytokine and low-density lipoprotein levels, while increasing the expression of Sirt1 and HO-1, which contributes to the mitigation of NAFLD progression[51]. In the quest to optimize therapeutic strategies, combining antioxidant treatments with MSC delivery stands out as a promising approach to addressing liver inflammation and offers a comprehensive solution to the challenges posed by obesity, prediabetes, and related complications such as NAFLD[48].

As the therapeutic landscape evolves, the potential of MSCs to mitigate hepatic inflammation in NASH has gained prominence by targeting key mediators. Importantly, the levels of significant contributors to hepatic inflammation, such as TNF-α, tissue inhibitor of metalloproteinases-1, and matrix metalloproteinase-12, were decreased following MSC intervention in NASH mice, thereby effectively reducing inflammation[44]. Moreover, MSC treatment has shown promise in delaying the onset of NASH in obese mice. This protective effect appears to stem from limiting the growth of proinflammatory lymphocyte subgroups and maintaining anti-inflammatory profiles, rather than reversing metabolic syndrome, thus aiding in the mitigation of NASH[52,53]. Another discovery was that MSC transplantation inhibited NASH progression by reducing hepatic inflammation, as demonstrated by the decreased expression of the acute-phase protein serum amyloid A, inflammation-associated markers such as lipocalin 2, and the proinflammatory cytokine TNF-α [54,55]. The ability of ADSCs to hinder NASH progression by mitigating IL-17-mediated and other inflammatory effects underscores their therapeutic potential, showing outcomes comparable to those of both NASH-specific uncultured adipose tissue-derived stromal cells (u-ADSCs) and wild-type u-ADSCs[56,57]. An integrated approach, employing either a combination of MSCs and MSC-EVs or solely MSC-EVs led to a noticeable increase in the number of anti-inflammatory macrophages in the liver, showing their robust immunomodulatory potency in NASH[45,49,58]. From a mechanistic standpoint, MSC-centric treatments exert their anti-inflammatory effects through diverse mechanisms, including modulating the levels of inflammatory cytokines and altering macrophage phenotypes. MSC-Exos promoted anti-inflammatory macrophage phenotypes both *in vitro* and *in vivo*, thus emphasizing their therapeutic potential in NASH based on moderating inflammation and restoring cellular balance[59]. Hepatoprotective effects were observed with MSCs from various sources; for instance, both stem cell-derived conditioned medium and amnion-derived MSCs preserved hepatocyte health and inhibited proinflammatory macrophage activation[60,61]. Complementing these findings, antioxidant-fortified MSCs have shown promise in reducing inflammation and alleviating fatty liver conditions associated with diet-triggered obesity[48,62]. Emerging research underscores the transformative potential of MSC-based treatments in mitigating hepatic inflammation in NASH.

MSC intervention regulates oxidative stress and ER stress in NAFLD/NASH

In NAFLD, the increased production of ROS causes damage to cellular proteins and DNA, with persistent oxidative stress subsequently leading to cell injury and apoptosis. Concurrently, the accumulation of fatty acids induces ER stress, which interferes with protein folding and, over time, impairs liver function. Importantly, MSC therapies offer significant benefits in these areas. In studies of NAFLD rats and palmitate-induced HepG2 cells, treatment with MSCs adjusted the intracellular calcium balance through SERC modulation, thereby reducing ER stress and enhancing metabolic function [34]. Similarly, transplantation of ADSCs provides dual benefits by alleviating abnormalities in lipid metabolism and oxidative stress in NAFLD[41]. Both *in vivo* and *in vitro* studies of diabetes-related NAFLD involving the implantation of BMSCs have revealed significant mitochondrial transfer. The recipient steatotic cells demonstrated increased OXPHOS activity, ATP production, and membrane potential, and reduced ROS levels[35]. Additionally, interventions using MSC-CMs have shown enhanced antioxidant capabilities and improved mitochondrial function *via* SIRT1-mediated effects in T2DM/NAFLD[50]. Moreover, treatment with MSC-Exos significantly reduced ROS and oxidative stress by targeting KEAP-1 *via* miR-24-3p in NAFLD[37].

In the pathogenesis of NASH, oxidative stress and ER stress play interconnected and complementary roles, collectively driving the progression of disease. Recent advancements in therapeutic research have highlighted the potential of MSC-centered treatments and emphasized their effectiveness in attenuating oxidative stress and its subsequent effects on NASH. Specifically, MSC therapies have shown their potential for enhancing oxidative capacity to restore metabolic and tissue balance[44,53]. Delving further into this therapeutic framework, hUC-MSC-Exos have been shown to significantly suppress NASH-induced oxidative stress by reducing malondialdehyde, CYP2E1, and ROS levels; enhancing superoxide dismutase and glutathione activities in hepatocytes; increasing the p-nuclear factor erythroid 2-related factor2/nuclear factor erythroid 2-related factor2 protein ratio; and increasing NQO-1 expression[45]. In a parallel therapeutic approach, combined treatment involving BMSCs and BMSC-Exos demonstrated a significant antiapoptotic effect, as indicated by a substantial decrease in the Bax/Bcl2 ratio and increased expression of mitochondrial mitophagy-related genes, including Parkin, PINK1, ULK1, BNIP3 L, ATG5, ATG7, and ATG12 in NASH[47]. Additionally, exosomes derived from curcumin-preconditioned MSCs significantly downregulated the expression of ASK-JNK-BAX genes involved in mitochondrial stress and apoptosis[63]. These findings underscore the complex interplay between oxidative stress, ER stress, and MSC-driven interventions, as well as the effectiveness of these interventions in addressing NASH.

MSC therapy: A potential solution for liver fibrosis in NAFLD/NASH

Fibrosis plays a crucial role in the pathogenesis of NAFLD/NASH. Extended liver damage, particularly from excessive fat accumulation, triggers the activation of specialized stellate cells that produce collagen, leading to fibrosis. Emerging research has consistently highlighted the therapeutic potential of MSCs in ameliorating liver fibrosis in NAFLD/NASH. For instance, MSC therapies have led to significant improvements in NASH, with a nearly 50% reduction in collagen content[33,44]. This evidence is supported by other findings that emphasize the therapeutic benefits of MSC transplantation[53,55]. Furthermore, both ADSC-EVs and ADSCs represent a comprehensive strategy to alleviate NASH. Specifically, ADSC-EVs have been found to decelerate NAFLD progression by delivering antifibrotic miR-223-3p, which consequently reduces *E2F1* expression[42]. In certain studies, ADSC treatments have been shown to effectively inhibit the progression of NASH fibrosis by targeting IL-17-mediated inflammation, a key factor in the activation of hepatic stellate cells (HSCs)[57]. Interestingly, both NASH-derived u-ADSCs and wild-type u-ADSCs show promise in preventing and reducing fibrosis in NASH[56].

A further promising therapeutic avenue involves modulating the gut-liver axis; a conditioned medium derived from stem cells from human exfoliated deciduous teeth (SHED-CM) successfully prevented fibrosis progression in a NASH mouse model[61]. Similarly, ADSC-EVs significantly reduced fiber accumulation and Kupffer cell and HSC activation in rats with NASH[49]. However, the therapeutic outcomes of treatments derived from MSCs are not universally consistent. For instance, there was a significant initial 12.4-fold increase in molecular fibrosis associated with NASH, which returned to normal after three months of treatment with MSC-Exos-curcumin. In contrast, treatments using only MSC-Exos resulted in a temporary 40%-50% reduction in fibrosis, which unfortunately rebounded after three months[63]. Another study suggested that treatment with MSC-EVs effectively reduced liver fibrosis in the NASH mouse model, despite an increase in profibrotic M2 macrophage polarization[58]. Taken together, these findings highlight the immense therapeutic potential of MSCs and their derivatives in treating liver fibrosis associated with NAFLD/NASH, although their effectiveness can vary in magnitude and duration.

MSCs and MSC-derived secretory factors play a crucial role in enhancing insulin sensitivity, reducing hepatic lipid accumulation, and moderating inflammatory responses. Additionally, they effectively counteract oxidative stress and ER stress, which are central contributors to NASH progression, while exhibiting anti-fibrotic capabilities that inhibit disease progression. Given the findings from both *in vitro*[34,35,37,39,42,43,45,46,50,59,63,64] (Table 1) and *in vivo*[34-47,49-61,63-66] (Table 2) studies, MSC-based therapies stand out as promising strategies, offering an integrative solution to address and possibly reverse the multifaceted challenges of NAFLD/NASH.

DISCUSSION

In the context of NAFLD/NASH treatment, MSCs have emerged as a promising therapeutic avenue due to their unique cellular properties and demonstrated efficacy. They can be applied to address a range of pathological challenges, including glycemic-lipid metabolism, inflammation, oxidative stress, ER stress, and fibrosis. Emerging research has consistently highlighted the potential of MSCs in inhibiting the progression of NAFLD/NASH. Importantly, these mechanisms are not biologically isolated but exhibit intersecting and complementary mechanisms, which enhance the effects of one another. For instance, MSC intervention can directly alleviate fat accumulation in glycemic lipid metabolism, subsequently reducing hepatic inflammatory responses[50]. This reduction in inflammation further leads to the suppression of oxidative stress[45]. Furthermore, the intrinsic antioxidative capabilities of MSCs may provide additional reinforcement against oxidative challenges and aid in alleviating ER stress caused by excessive protein accumulation, thereby promoting the functional balance of hepatocytes[34]. Additionally, MSCs can indirectly inhibit the activation of HSCs by impacting inflammation and glycemic-lipid metabolism, thus preventing the onset of fibrosis[44]. Consequently, the multifaceted mechanisms of MSCs may synergize, creating a comprehensive, multilevel therapeutic approach for NAFLD/NASH patients.

Considering the complex and multifactorial nature of NAFLD/NASH, relying solely on MSC-based treatments may not adequately address the disease. Consequently, integrating MSCs with various strategies, such as pharmacotherapy, lifestyle modifications, gene therapy, cell therapy, and biomaterials, has emerged as a research priority, with the aim of developing a holistic approach to this disease. For instance, combining MSCs with specific anti-inflammatory and antioxidant drugs could enhance their therapeutic efficacy, potentially reducing drug dosages and associated side effects [63]. Adopting beneficial dietary habits, engaging in regular exercise, and implementing weight loss strategies are crucial for improving liver function in individuals with NAFLD/NASH[16]. Significantly, weight reduction directly contributes to decreased fat accumulation in the liver. Therefore, integrating MSC therapy with these lifestyle adjustments may synergistically improve the therapeutic outcomes of patients. Gene engineering provides renewed perspectives and innovative insights for NAFLD treatment[67], and its integration with MSC therapies opens up new therapeutic possibilities. Furthermore, combining MSCs with other cells with therapeutic potential or using biomaterials as delivery mechanisms may further refine and enhance the effectiveness of treatment[47,63]. These multifaceted strategies promise a more holistic, efficient, and tailored approach to treating NAFLD. However, the safety and efficacy of these integrated strategies require further clinical validation.

Although the use of MSCs for treating NAFLD/NASH is promising, practical applications still face a series of challenges and limitations. The variability in the therapeutic properties of MSCs associated with their origin is essential, yet comprehensive studies comparing their efficacy in treating NAFLD are lacking. This diversity necessitates careful research for optimal source selection[26]. Moreover, the survival and homing capabilities of MSCs are compromised under challenging conditions such as low oxygen tension, fluid pressure stress, and interactions with whole blood components postinjection. This process is further complicated by hypoxia, oxidative stress, and inflammation at targeted sites[68]. Alarmingly, significant concerns regarding potential risks, including tumorigenesis and adverse immune reactions must be considered. Certain MSCs, particularly BMSCs that have not been genetically modified, may exhibit chromosomal abnormalities even during early passages, potentially leading to the formation of malignant tumors[69]. Furthermore, considering the relationship between the injection frequency, dosage, and therapeutic effect of MSCs in maintaining long-term efficacy is crucial. Moreover, determining whether single or cotreatments with MSCs might have adverse effects is essential for their appropriate application in treating NAFLD[70].

MSC-EV or MSC-Exo therapy is superior to cell therapy in terms of safety, efficacy, and versatility, and reduces the potential risks of long-term mal-differentiation of engrafted cells and tumor formation[70]. However, several challenges must be addressed before this strategy can be used in clinical practice. For instance, the rapid clearance of MSC-Exos from the body might limit their long-term therapeutic effects[71]. In addition, the heterogeneity of MSC-Exos resulting from different culture conditions and cell passages poses another challenge. Therefore, standardized isolation protocols and

Table 1 Mesenchymal stem cells treatments for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis *in vitro*

Cell sources	Passage number	Cell models	Biological effects
Rat BM MSCs	P3-4	HepG2 cells	rMSCs alleviated cellular lipotoxicity and metabolic disturbance, primarily by regulating ER stress and calcium homeostasis *via* SERCA[34]
Mouse BM MSCs	P5-10	HepG2 cells	mBMSCs restored disordered glucose and lipid metabolism, as well as mitochondrial dysfunction in T2DM/NAFLD[35]
Human UC MSCs derived miR-24-3p	Not reported	Primary hepatocytes	hUC-MSC derived miR-24-3p suppressed lipid accumulation, ROS generation, and inflammatory response through targeting KEAP-1 signaling [37]
Human UC MSCs derived miR-627-5p	P3	L-02 cells	hUC-MSC-derived miR-627-5p improved glucose and lipid metabolism by targeting FTO[39]
Mouse AD MSCs derived miR-223-3p	P2 or above	NCTC1469 cells	mADSC-EV-derived miR-223-3p exhibited suppressive effects on lipid accumulation and liver fibrosis by inhibiting the target gene *E2F1*[42]
Human MenSCs	P2-3	L-02/AML12 cells	Hepatocyte growth factor secreted by MenSCs in NAFLD promoted hepatic glycogen storage and attenuated lipid accumulation through the downregulation Rnf186[43]
Human UC MSCs derived Exos	Not reported	HepG2/AML12 cells	hUC-MSC-Exos attenuated steatosis in hepatocytes and inhibited oxidative stress in NASH[45]
Mouse AD MSCs	P5-6	Murine hepatocyte cell line H2.35	mADSCs treatment alleviated lipotoxicity-induced apoptosis in steatotic hepatocytes by activating the Notch signaling pathway[46]
Human UC MSCs derived CM	Not reported	L-02 cells	hMSC-CM enhanced liver mitochondrial function while reducing inflammation and apoptosis by upregulating SIRT1[50]
Human UC MSCs derived Exos	P4-7	HepRG cells	hUC-MSC-Exos reduced inflammatory cytokines by inducing macrophage anti-inflammatory phenotypes[59]
Human CB MSCs derived Exos with curcumin	Not reported	HepG2 cells	MSC-Exos with curcumin improved cell viability and inhibited lipogenesis, while the anti-apoptotic pathway involved the downregulation of *ASK1*, *JNK*, and *BAX* genes[63]
Human UC MSC derived Exos	P3-4	L-02/AML12 cells	MSC-Exos inhibit lipid accumulation by promoting the β-oxidation of fatty acids and suppressing fatty acid synthesis[64]

MSCs: Mesenchymal stem cells; BM: Bone marrow; UC: Umbilical cord; AD: Adipose- derived; CB: Cord blood; Exos: Exosomes; EVs: Extracellular vesicles; T2DM: Type 2 diabetes mellitus; MenSCs: Menstrual blood-derived stem cells; mADSCs: Mouse adipose-derived stem cells; NAFLD: Non-alcoholic fatty liver disease.

defined culture conditions are required to produce more homogenous populations of MSC-Exos[72,73]. Another issue that requires resolution is the long-term storage, preservation, and transportation of exosomes, including whether lyophilization alters the characteristics of exosomes[70,73]. Moreover, current efforts focus on using encapsulation to increase longevity in the body[74]. For example, with advancements in bioengineering and cellular manipulation technologies, the upcoming trend regarding exosome utilization will involve engineering exosomes to be more specific and applicable in highly complicated areas of medicine[75].

MSCs and their derived secretions have shown significant potential benefits for the treatment of NAFLD/NASH. However, research on the treatment of NAFLD with MSCs is still in the exploratory stage prior to widespread clinical application. The number of studies on treating NAFLD with MSCs is small, and most of these studies are based on rodents. Thus, the scope of research needs to be expanded further using larger animals[70]. In addition, the specific therapeutic mechanisms and targets of MSCs and intrinsic liver cells are unclear; questions such as how MSCs aid in repairing damaged liver, regulate immune responses, and interact with other liver cells, such as HSCs and Kupffer cells, should be answered[23]. Importantly, the different progression stages of NAFLD and the specific conditions of patients may require different treatment strategies[46]. Further study is required to investigate whether MSCs retain the same therapeutic properties in clinical settings as they do *in vivo* and *in vitro*.

CONCLUSION

In summary, MSCs offer a promising therapeutic direction for NAFLD/NASH through the alteration of underlying molecular pathways, including glycolipid metabolism, inflammation, oxidative stress, ER stress, and fibrosis. By thoroughly understanding their mechanisms of action and integrating them with other treatment modalities, more effective and safer therapeutic strategies may be developed. As we advance in this field of research, it is imperative that we continuously monitor the outcomes of MSCs in clinical trials, ensuring positive results not only in laboratory settings but also in real-world clinical environments.

Table 2 Mesenchymal stem cells treatments for non-alcoholic fatty liver disease/non-alcoholic steatohepatitis *in vivo*

MSC source	Passage number	Animal models	Other instructions	Biological effect
Mouse CB MSCs	P5-8	Mouse	1×10^6 cells/mouse injected (i.v.) at weeks 21 and 23	mMSCs transplantation decreased high-fat-induced weight gain, expansion of subcutaneous adipose tissue, steatosis, lobular inflammation, and liver fibrogenesis[33]
Rat BM MSCs	P3-4	Rat	2×10^6 cells/rat injected (i.v.) at weeks 18 and 20	rMSCs administration improved lipid metabolism and insulin sensitivity, and inhibited ER stress in the liver[34]
Mouse BM MSCs	P5-10	Mouse	1×10^7 cells/kg body weight injected (i.v.)	mBMSCs restored disordered glucose levels, reduced fat accumulation, and corrected mitochondrial dysfunction in mice with diabetes-associated NAFLD[35]
Human UC MSCs	P5	Rat	1×10^6 cells/rat injected (i.v.) at weeks 1 and 5	hUC-MSCs in combination with liraglutide improved glycolipid metabolism, insulin resistance, and liver injury in T2DM/NAFLD rats by downregulating TLR4/NF-κB inflammatory pathway and ameliorating oxidative stress[36]
Human UC MSCs derived miR-24-3p	Not reported	Mouse	120 μg/mouse injected (i.v.) weekly for 16 weeks	hUC-MSC-derived miR-24-3p alleviated lipid accumulation, inflammation, and oxidative stress in NAFLD[37]
Human UC MSCs	P3	Mouse	1×10^6 cells/mouse injected (i.v.) once a week for 6 weeks	hUC-MSCs improved glucose homeostasis and lipid metabolism, and alleviated hepatic steatosis and liver damage in obese T2DM/NAFLD mice [38]
Human UC MSCs derived miR-627-5p	P3	Rat	100 μg/rat injected (i.v.) once a week for 2 months	hUC-MSC-derived miR-627-5p improved glucose and lipid metabolism, and alleviated liver damage in NAFLD[39]
Rat AD MSCs	P3-15	Rat	2×10^6 cells/rat injected (p.v.)	rADSCs improved liver function and lipid metabolism, thereby exerting hepatoprotective effects[40]
Rat AD MSCs	P3	Rat	2×10^6 cells/rat injected (p.v.)	rADSCs improved liver function; reduced lipid accumulation, oxidative stress, and inflammation; and decelerated the progression of NAFLD in the rat model[41]
Mouse AD MSCs derived miR-223-3p	P2 or above	Mouse	100 μg/mouse injected (i.v.) twice a week for last 6 weeks	mADSC-EV-derived miR-223-3p attenuated lipid accumulation and fibrosis by negatively regulating *E2F1* expression[42]
Human MenSCs	P2-3	Mouse	5×10^5 cells/mouse injected (i.v.) at weeks 16, 19, and 22	Hepatocyte growth factor secreted by MenSCs in fatty liver diseases promoted hepatic glycogen storage and attenuated lipid accumulation in NAFLD[43]
Human BM MSCs	P6-15	Mouse	$(0.9\text{-}1) \times 10^6$ cells/mouse *via* splenic injection	hBMSCs reduced hepatic lipid content, inflammation, and fibrosis, as well as restored metabolic and tissue homeostasis, by donating human mitochondria to mouse hepatocytes[44]
Human UC MSCs derived Exos	Not reported	Mouse	100 μg/mouse injected (i.v.) twice a week for final 2 weeks	hUC-MSC-Exos attenuated steatosis, inflammatory responses, and oxidative stress in hepatocytes *via* the Nrf2/NQO-1 pathway[45]
Mouse AD MSCs	P5-6	Mouse	1×10^5 cells/mouse *via* splenic injection twice every 2 weeks for 12 weeks	mADSCs reduced apoptosis of steatotic hepatocytes and restored cellular proliferation by activating Notch signaling[46]
Rat BM MSCs/ Rat BM MSCs derived Exos	P4	Rat	1×10^6 cells/mouse injected (i.v.)/15/30/120 μg/kg body weight injected (i.v.) twice per week for 6 weeks	rBMSCs and rBMSC-Exos reduced lipid accumulation, hepatotoxicity, oxidation, and hepatocyte apoptosis, and activated mitochondrial mitophagy[47]
Human AD MSCs/ Human AD MSCs derived EVs	P4	Mouse	1×10^6 cells/mouse injected (i.v.)/ 1.0/2.5/5.0 μg injected (i.v.) at week 12	hADSCs or hADSC-EVs exhibited anti-inflammatory and anti-fibrotic effects in the NASH model[49]
Human UC MSCs derived CM	Not reported	Mouse	200 μL cells/mouse injected (i.v.) every 3 days for 2 months	hMSC-CM improved glucose tolerance, insulin sensitivity, and mitochondrial function, and alleviated liver dysfunction, lipid accumulation, inflammation, and apoptosis by upregulating SIRT1[50]

Human BM MSCs	Not reported	Mouse	1×10^7 cells/mouse injected (p.v.)	hMSCs decreased the inflammatory cytokines, LDL levels, IR, and oxidative stress in NAFLD with T2DM[51]
Mouse BM MSCs	P3	Mouse	0.5×10^6 cells/mouse injected (i.v.) at weeks 33 and 37	mMSCs administration prevented the onset of NASH in obese mice[52]
Murine CB MSCs	P5-8	Mouse	1×10^6 cells/mouse injected (i.v.) at weeks 6 and 7	mMSCs reduced weight loss, hepatic lipid peroxidation, steatosis, ballooning, lobular inflammation, and fibrogenesis in NASH[53]
Human BM MSCs	Not reported	Mouse	1.5×10^6 cells/mouse injected (i.v.) at day 42	Hepatocyte-like cells derived from hBMSCs attenuated liver lipid accumulation and inflammation, and enhanced the regenerative capacity of the liver in NASH[54]
Human UC MSCs	Not reported	Mouse	1×10^6 cells/mouse injected (i.v.) at week 10	hMSCs alleviated hepatic steatosis, inflammation, and fibrosis, and reversed microbiome and metabolome disorders[55]
Uncultured mouse AD MSCs	Not reported	Mouse	$1 \times 10^6/7.5 \times 10^5$ cells/mouse *via* splenic injection at weeks 24 and 26	u-ADSCs derived from a NASH mouse model and wild-type mice had similar effects in reducing inflammation and fibrosis in NASH[56]
Mouse AD MSCs	Not reported	Mouse	1×10^5 cells/mouse *via* splenic injected at weeks 4 and 8	mADSCs administration prevented the progression of NASH fibrosis by suppressing IL-17-mediated inflammation[57]
Human ESC MSCs derived EVs	Not reported	Mouse	1 and 10 μg/50 μL/mouse (i.p.) every other day for last 4 weeks	hMSC-EVs increased the number of anti-inflammatory M2 macrophages and suppressed fibrosis in NASH[58]
Human UC MSCs derived Exos	P4-7	Mouse	20 mg/kg body weight injected (i.v.) twice a week for 6 weeks	hUC-MSC-Exos regulated the anti-inflammatory phenotype of macrophages and reversed PPARα protein expression in liver cells[59]
Human AM MSCs derived EVs	Not reported	Rat	15 μg/kg body weight injected (i.v.) at weeks 3 and 4	AMSC-EVs alleviated inflammation and fibrosis in a NASH rat model[60]
Human SHEDs derived CM	P8-12	Mouse	0.5 mL cells/mouse injected (i.v.) once a week from week 10 to 12	SHED-CM treatment inhibited liver fibrosis, inflammation, and parenchymal cell apoptosis in NASH[61]
Human CB MSCs derived Exos with curcumin	Not reported	Mouse	15 μg/kg body weight injected (i.v.)	Exosomes derived from curcumin-preconditioned MSCs ameliorated NASH, protected against recurrence, and regulated inflammatory response, oxidative stress, and mitochondrial-dependent apoptosis[63]
Human UC MSC derived Exos	P3-4	Mouse	10 mg/kg body weight injected (i.v.) for last 4 weeks	hUC-MSC-Exos effectively reduced lipid deposition and improved liver function in an NAFLD mouse model *via* CAMKK1-mediated regulation of lipid homeostasis[64]
Rat AD MSCs stimulated with LPS	P3-5	Rat	1.5×10^6 cells/rat injected (i.v.) at week 8 for 6 weeks	ADSCs stimulated with LPS showed potential to alleviate NAFLD by reducing the expression of inflammatory genes and the levels of ROS[65]
Human UC MSCs	P5	Mouse	1.5×10^6 cells/mouse injected (i.v.) at week 32	hUC-MSCs administration alleviated obesity, improved glucose metabolism, and reduced hepatic steatosis, inflammation, and fibrosis in NASH[66]

MSCs: Mesenchymal stem cells; BM: Bone marrow; UC: Umbilical cord; AD: Adipose- derived; ESC: Embryonic stem cells; AM: Amniotic membrane; CM: Conditioned medium; CB: Cord blood; Exo: Exosome; EVs: Extracellular vesicles; SHED: Stem cells derived from human exfoliated deciduous teeth; LPS: Lipopolysaccharide; T2DM: Type 2 diabetes mellitus; i.v.: Intravenous; p.v.: Portal vein; i.p.: Intraperitoneal; MenSCs: Menstrual blood-derived stem cells; LDL: Low-density lipoprotein; Nrf2: Nuclear factor erythroid 2-related factor2; mADSCs: Mouse adipose-derived stem cells; ER: Endoplasmic reticulum; NASH: Non-alcoholic steatohepatitis; ROS: Reactive oxygen species; NAFLD: Non-alcoholic fatty liver disease; IL: Interleukin; LPS: Lipopolysaccharide; PPAR: Peroxisome proliferator-activated receptor.

FOOTNOTES

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