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The Role of Bone Marrow Mesenchymal Stem Cells and Adipose Tissue-Derived Stem Cells in the Treatment of Liver Failure: A Literature Review

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ABSTRACT Liver disease is a major health problem that endangers human health worldwide. Stem cells have the unique ability to morph or differentiate into different types of cells within the body. In this way, stem cells can be used to seek out damaged liver tissue and regenerate the organ itself. Mesenchymal stem cells are multipotent stem cells that can self-renew and differentiate into different cell types. In other words, mesenchymal stem cells can become a variety of different cell types including adipose tissue, cartilage, muscle, tendon/ligament, bone, neurons, and hepatocytes. Many studies have shown that Mesenchymal stem cells play an essential role in liver recovery, and further research has verified the preliminary effectiveness and safety of these therapies. types of liver disease that are most suitable for MSC application should be determined, and the preparation and engraftment of MSCs should be standardized. Stem cell-based therapies will emerge as an effective treatment strategy for liver diseases in now and the future. Researchers conduct an examination of articles that are in accordance with the issue to be studied. Articles used in literature review are obtained through the database of international journal providers through PubMed, we investigated six clinical studies and discussed what happened in these clinical studies and the extent of the effectiveness of stem cells in treatment and whether the degree of liver disease had a role in the effectiveness of stem cells, we also discussed the mechanism of stem cells in treatment. One of six articles proved that Zeaxanthin dipalmitate (ZD) could enhance the defensive abilities against adverse stresses of human adipose-derived mesenchymal stem cells, One of six articles proved that infusion of allogeneic bone marrow-derived MSCs improving liver function and decreasing the incidence of severe infections. The rest articles proved that MSCs both Bone Marrow Stem cells (BMSCs) and Adipose Derived Stem Cells (ADSCs) are promising therapeutic agents for the liver fibrosis and cirrhosis treatment. In this review, we suggest that formulating and following treatment, Further studies are needed to determine the related mechanisms to enhance MSC efficacy.

INDEX TERMS Mesenchymal stem cells, Adipose Derived Stem Cells, Bone Marrow Stem cells.

I. INTRODUCTION

Stem cells are operationally defined as cells that have the potential for unlimited or prolonged self-renewal, as well as the ability to give rise to at least one type of mature, differentiated cells [1].

A. STEM CELLS CLASSIFICATION

Totipotent Cells are the most undifferentiated cells and are found in early development. A fertilized oocyte and the cells of the first two divisions are totipotent cells, as they differentiate into both embryonic and extraembryonic tissues, thereby forming the embryo and the placenta [2] (FIGURE 1).

Pluripotent Cells are able to differentiate into cells that arise from the 3 germ layers – ectoderm, endoderm, and mesoderm from which all tissues and organs develop [3]. Multipotent Cells are found in most tissues and differentiate into cells from a single germ layer [4]. Mesenchymal stem cells (MSCs) are the most recognized multipotent cell. They can be derived from a variety of tissue including bone marrow, adipose tissue, bone, Wharton's jelly, umbilical cord blood, and peripheral blood [5].

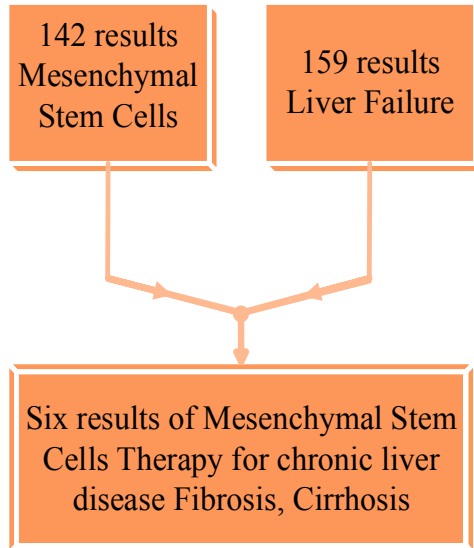


FIGURE 1. The Process of retrieving literature articles

Unipotent Cells can self-renew and differentiate into only one specific cell type and form a single lineage such as muscle stem cells, giving rise to mature muscle cells and not any other cells [6]. Embryonic Stem Cells ESCs are pluripotent, derived from the inner cell mass of the blastocyst, a stage of the pre-implantation embryo, 5–6 days post-fertilization [7]. Adult Stem Cells are derived from adult tissue. Examples include MSCs as well as stem cells derived from placental tissue such as human amnion epithelial cells. These cells have been shown to be anti-inflammatory and augment repair of animal models of injury. They have limited differentiation capacity although these cells have been differentiated into tissue from different germ cell layers in vitro [8].

B. MESENCHYMAL STEM CELLS (MSCS)

Mesenchymal stem cells (MSCs), also referred to as mesenchymal stromal cells, are adult stem cells capable of self-renewal and multilineage differentiation [9]. They were originally found in the bone marrow [10], but they were later identified in other tissues including adipose tissue, muscle, peripheral blood, hair follicles, teeth, placenta, and umbilical cord [11]. MSCs are heterogeneous and polyclonal cells, with at least three subpopulations defined based on morphology. Type I MSCs are spindle-shaped proliferating cells resembling fibroblasts. Type II MSCs are large, flat, epithelial-like cells, which are more senescent than type I cells

and feature visible cytoskeletal structures and granules. Finally, type III MSCs are small round cells with a high capacity for self-renewal [12]. The heterogeneity of MSCs can be considered beneficial in that it ensures that some therapeutically active cells are present, but it reduces the maximum potential efficacy because some of the cells are inactive. However, even monoclonal MSCs become heterogeneous during expansion [13]. Although MSCs may exhibit different characteristics depending on their tissue of origin, they must meet the three minimal criteria defined by the International Society for Cellular Therapy (ISCT) (I) MSCs able to plastic adherence; (II) able to differentiate into cartilage, bone, and fat tissue in vitro; and (III) express the cluster of differentiation (CD) surface markers CD73, CD90, and CD105, but not CD11b, CD14, CD19, CD34, CD45, or HLA-DR [14]. Several other markers may be more specific but are only detected in certain MSC isolates or subpopulations. These include stage-specific embryonic antigen-4 (SSEA-4), stem cell antigen-1 (SCA1), nestin, CD44, CD146, CD166, and CD271 [15, 16, 17, 18, 19].

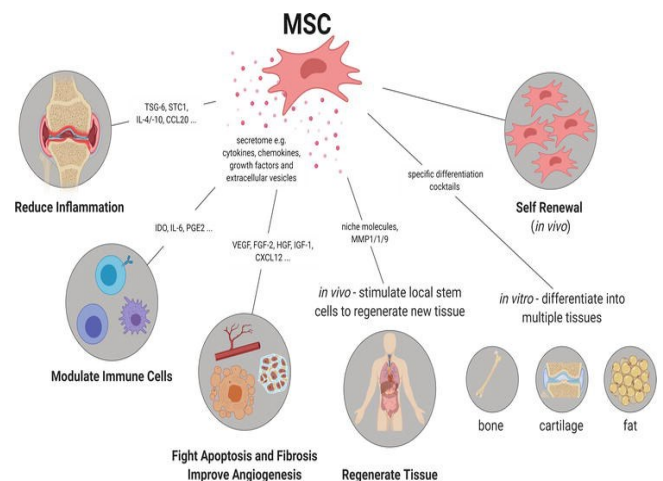


FIGURE 2. Stem Cell properties, Self renewal and differentiation into multiple tissues and organs

Based on data from PubMed database Mesenchymal Stem Cells has been suggested to be a promising therapy for liver diseases. But there are many obstacles that hinder the use of stem cells, especially in clinical applications, as the different degree of liver disease may determine the ability and effectiveness of stem cells. From this, it is necessary to conduct an in-depth study to find out mechanisms by which MSCs play a therapeutic role in liver disease especially chronic liver disease. Therefore, we investigated 6 clinical studies and discussed what happened in these clinical studies and the extent of the effectiveness of stem cells in treatment and whether the degree of liver disease had a role in the effectiveness of stem cells, we also discussed

the mechanism of stem cells in treatment. Mesenchymal stem cells have become one of the most promising means in treating many diseases, whether they are immune diseases or other diseases. Therefore, it was found that Mesenchymal stem cells have a leading role in treating liver diseases. But does the use of stem cells in treatment instead of using traditional treatment in treating liver diseases still needs clarification.

C. MESENCHYMAL STEM CELLS IN LIVER DISEASES

liver disease presents a major threat to human health. Many stimuli, such as viral hepatitis, alcohol abuse, drugs, metabolic diseases, and autoimmune attack, can trigger chronic/acute liver injury and inflammation, which result in liver failure, cirrhosis and associated hepatocellular carcinoma. Liver transplantation is the only effective treatment for liver cirrhosis and liver failure. However, the number of suitable donor organs PubMed, from 2019-2022, Clinical Trials only. Author opens www.PubMed.com. Researchers wrote keywords according to MESH (Medical Subject Heading) namely "Mesenchymal Stem Cells", "Liver Failure", and selected full text.

1. Inclusion Criteria Population or sample is Liver failure (acute and chronic liver disease).
2. Exclusion Criteria Population or sample other than Liver failure (acute and chronic liver disease).

is very limited. [16, 20, 21]. Cell-based therapy using mesenchymal stem cells (MSCs) have been confirmed to have beneficial effects on liver fibrosis in several basic and clinical studies [17, 22, 23, 24, 25, 26, 27, 28] (FIGURE 3).

II. METHODS

Researchers conduct an examination of articles that are in accordance with the issue to be studied. Determination of literature search keywords (search string based on PI (E)COT framework (P=patient/problem; I/E=exposure/implementation; C= control/comparison intervention, O=outcome, T=time) because a good question will help determine the scope of the review and help the strategy of finding the article. Articles used in literature review are obtained through the database of international journal providers through

III. RESULTS

TABLE 1 shows the clinical studies using MSCs both BMSCs and ADSCs therapy in liver fibrosis and cirrhosis diseases. Yingxia Liu *et al* [29] found that zeaxanthin dipalmitate (ZD) could enhance the defensive abilities against adverse stresses of human adipose-derived mesenchymal stem cells (hADMSCs) in vitro and increase their therapeutic outcomes of acute liver failure after transplantation in vivo. Treatment with ZD dramatically improved cell survival and suppressed apoptosis, inflammation, and reactive oxygen species (ROS) production of hADMSCs through the PKC/Raf-1/MAPK/NF- κ B pathway to maintain a reasonably high expression level of microRNA-210 (miR-210). Ming Shi *et al* [30] who implemented treatment as patients were treated with UC-MSCs. No significant side effects were observed during the trial. The UC-MSC transfusions significantly increased the survival rates in Acute-on-chronic liver failure (ACLF) patients; reduced the model for end-stage liver disease scores; increased serum albumin, cholinesterase, and prothrombin activity; and increased platelet counts. Serum total bilirubin and alanine aminotransferase levels were significantly decreased after the UC-MSC transfusions. Fernando *et al* [31], who implemented a Phase I-II Randomized Clinical Trial which enrolled 9 cirrhotic patients from 2018 to 2020, regardless of the etiology. The patient who completed the entire MSC protocol showed a significant improvement in CP (C-14 to B-9), MELD (32 to 22), and ACLF (grade 3 to 0). Bing-Liang *et al* [32], who implemented open-label, nonblinded randomized controlled study on patients with HBV-related ACLF. The experimental group (n = 56) was infused weekly for 4 weeks with 1.0 to 10×10^5 cells/kg allogeneic bone marrow derived MSCs and then followed for 24 weeks. Results from this study showed that Peripheral infusion of allogeneic bone marrow-derived MSCs is safe and convenient for patients

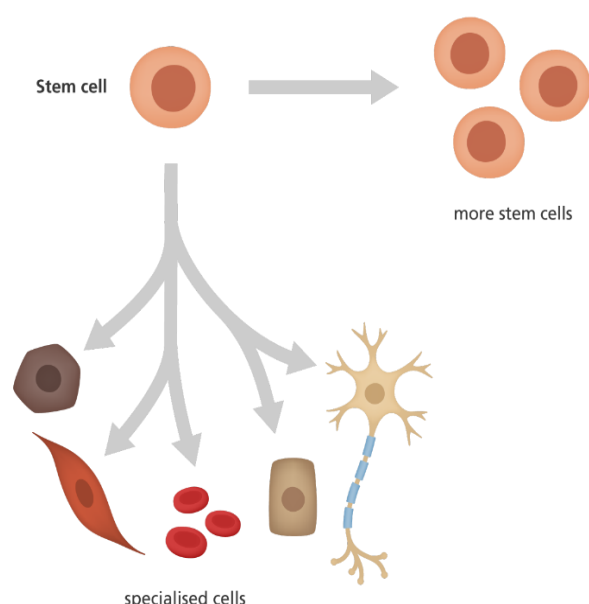


FIGURE 3. Properties of MSCs and their mode of action, they reduce inflammation, promote neo-angiogenesis, and prevent apoptosis and fibrosis. Further, they stimulate local stem cells to develop new tissue

TABLE 1
Clinical studies using MSCs both BMSCs and ADSCs therapy in liver fibrosis and cirrhosis.

Authors	Title	Methods and procedures	Result
Yingxia Liu et al.[29]	Precise Regulation of miR-210 Is Critical for the Cellular Homeostasis Maintenance and Transplantation Efficacy Enhancement of Mesenchymal Stem Cells in Acute Liver Failure Therapy	Stem cell viability was evaluated by the MTT assay. After treatments, cells were washed by sterile PBS thrice and then incubated with 5 mg/ml MTT for 4 h, and subsequently dissolved in dimethyl sulfoxide (DMSO; Sigma-Aldrich). The absorbance of MTT was measured at 570 nm, and pure DMSO was set as blank.	zeaxanthin dipalmitate (ZD) could enhance the defensive abilities against adverse stresses of human adipose-derived mesenchymal stem cells (hADMSCs) in vitro and increase their therapeutic outcomes of acute liver failure after transplantation in vivo. Treatment with ZD dramatically improved cell survival and suppressed apoptosis, inflammation, and reactive oxygen species (ROS) production of hADMSCs through the PKC/Raf-1/MAPK/NF-κB pathway to maintain a reasonably high expression level of microRNA-210 (miR-210).
Ming Shi et al. [30]	Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients	A total of 43 ACLF patients were enrolled for this open-labeled and controlled study; 24 patients were treated with UC-MSCs, and 19 patients were treated with saline as controls. UC-MSC therapy was given three times at 4-week intervals. The liver function, adverse events, and survival rates were evaluated during the 48-week or 72-week follow-up period.	No significant side effects were observed during the trial. The UC-MSC transfusions significantly increased the survival rates in Acute-on-chronic liver failure (ACLF) patients; reduced the model for end-stage liver disease scores; increased serum albumin, cholinesterase, and prothrombin activity; and increased platelet counts. Serum total bilirubin and alanine aminotransferase levels were significantly decreased after the UC-MSC transfusions. UC-MSC transfusions are safe in the clinic and may serve as a novel therapeutic approach for HBV-associated ACLF patients.
Fernando Comunello Schacher, et al. [31]	Bone Marrow Mesenchymal Stem Cells in Acute-on-Chronic Liver Failure Grades 2 and 3: A Phase I-II Randomized Clinical Trial	This is a randomized placebo-controlled phase I-II single center study, which enrolled 9 cirrhotic patients from 2018 to 2020, regardless of the etiology. The control group (n = 5) was treated with standard medical therapy (SMT) and placebo infusion of saline. The intervention group (n = 4) received SMT plus 5 infusions of 1×10^6 cells/kg of BM-MSC for 3 weeks. Both groups were monitored for 90 days. A Chi-square test was used for qualitative variables, and the t-test and Mann-Whitney U test for quantitative variables. The Kaplan-Meier estimator was used to build survival curves. In this study, we followed the intention-to-treat analysis, with a significance of 5%.	Nine patients with a mean Child-Pugh (CP) of 12.3, MELD of 38.4, and CLIF-C score of 50.7 were recruited. Hepatitis C and alcohol were the main etiologies. The average infusion per patient was 2.9 and only 3 patients (2 in control and 1 in the BM-MSC group) received all the protocol infusions. There were no infusion-related side effects, although one patient in the intervention group presented hyponatremia and a gastric ulcer, after the third and fifth infusions, respectively. The survival rate after 90 days was 20% (1/5) for placebo versus 25% (1/4) for the BM-MSC. The patient who completed the entire MSC protocol showed a significant improvement in CP (C-14 to B-9), MELD (32 to 22), and ACLF (grade 3 to 0).
Bing-Liang Lin, et al. [32]	Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: A randomized controlled trial	110 patients with HBV-related ACLF were enrolled in this open-label, nonblinded randomized controlled study. The control group (n = 54) was treated with standard medical therapy (SMT) only. The experimental group (n = 56) was infused weekly for 4 weeks with 1.0 to 10×10^5 cells/kg allogeneic bone marrow derived MSCs and then followed for 24 weeks.	Peripheral infusion of allogeneic bone marrow-derived MSCs is safe and convenient for patients with HBV-related ACLF and significantly increases the 24-week survival rate by improving liver function and decreasing the incidence of severe infections
Hosny Salama, et al. [33]	Peripheral vein infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease	Forty patients with post-hepatitis C virus (HCV) end-stage liver disease were randomized into two groups: Group 1 (GI): 20 patients who received granulocyte colony-stimulating factor (G-CSF) for 5 days followed by autologous MSCs peripheral-vein infusion and group 2 (GII): 20 patients who received regular liver-supportive treatment only (control group).	First, autologous MSC infusion into a peripheral vein is as effective as the previously reported intrahepatic infusion. Second, MSCs have a supportive role in the treatment of end-stage liver disease, with satisfactory tolerability and beneficial effects on liver synthetic functions and hepatic fibrosis. Third, IV infusion of MSCs after G-CSF mobilization improves s-albumin within the first 2 weeks and prothrombin concentration and alanine Taransaminase after 1 month. According to the data from this current study and those previously reported by our group, we recommend further studies on patients' infusion with pure CD133 and CD34 followed by IV infusion of in vitro-differentiated MSCs within 1 week and another infusion after 3 months.

TABLE 1
(continued)

Authors	Title	Methods and procedures	Result
Mohie-Eldeen M Amer, et al. [34]	Clinical and laboratory evaluation of patients with end-stage liver cell failure injected with bone marrow-derived hepatocyte-like cells	Forty patients were included, divided into two groups. Group I: 20 patients receiving autologous bone marrow-derived mesenchymal stem cells stimulated to hepatic lineage. They were subdivided into two groups regarding the route of transplantation: intrasplenic (10) and intrahepatic (10). Group II: included 20 patients who received traditional supportive treatment. Patients were followed up using examination, laboratory investigations, abdominal ultrasonography, and evaluated by Child score, Model for End Stage Liver Disease score, fatigue scale, and performance status.	This study demonstrated the safety and short-term efficacy of autologous bone marrow-derived mesenchymal stem cell injection in liver cell failure. Further study is necessary to standardize the cell dose, determine the life span of the injected cells, and detect the appearance of long-term complications.

with HBV-related ACLF and significantly increases the 24-week survival rate by improving liver function and decreasing the incidence of severe infections. Hosny *et al* [33], who conducted infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease, patients who received granulocyte colony-stimulating factor (G-CSF) for 5 days followed by autologous MSCs peripheral-vein infusion. Results from this study showed that MSCs have a supportive role in the treatment of end-stage liver disease, with satisfactory tolerability and beneficial effects on liver synthetic functions and hepatic fibrosis. Mohie *et al* [34], who have made evaluation of patients with end-stage liver cell failure injected with bone marrow-derived hepatocyte-like cells, patients received autologous bone marrow-derived mesenchymal stem cells, Patients were followed up using examination, laboratory investigations, abdominal ultrasonography, and evaluated by Child score, Model for End Stage Liver Disease score, fatigue scale, and performance status. This study demonstrated the safety and short-term efficacy of autologous bone marrow-derived mesenchymal stem cell injection in liver cell failure. However, negative results were obtained in two clinical studies. *Mohamadnejad et al.*, reported that autologous BM-MSC transplantation (n=15) injected through the peripheral vein likely has no beneficial effect compared to controls (n=12). The absolute changes in Child-Pugh score, MELD scores, serum transaminase levels, and liver volumes did not differ between the MSC-treated and control groups at 12 months of follow-up [35]. MSCs can secrete various growth factors that encourage tumor cell growth and angiogenesis [36]. Previous experimental studies showed that the tendency for malignant formation depended on the number of passages. For example, in mouse MSCs, chromosomal abnormalities and transformation into malignant cells, such as sarcoma, have been observed after more than three passages [37].

IV. CONCLUSION

liver disease presents a major threat to human health. Many stimuli, such as viral hepatitis, alcohol abuse, drugs, metabolic diseases, and autoimmune attack, can trigger chronic/acute liver injury and inflammation, which result in liver failure, cirrhosis and associated hepatocellular carcinoma. Liver transplantation is the only effective treatment for liver cirrhosis and liver failure. However, the number of suitable donor organs is very limited. Cell-based therapy using mesenchymal stem cells (MSCs) have been confirmed to have beneficial effects on liver fibrosis in several basic and clinical studies. BMSCs inhibit hepatocyte necrosis by promoting liver cell proliferation. Therapeutic effects of BMSCs are mediated through soluble paracrine factors and cytokines that inhibit inflammatory responses and promote hepatocyte proliferation and regeneration. Conditioned medium from BMSCs cocultured with hepatocytes significantly improves the survival rate of ALF by preventing liver injury and promoting recovery of the liver structure. Compared with single-use hepatocyte transplantation or single-use BMSCs, cotransplantation of hepatocytes and BMSCs appears to have a better treatment effect on ALF. ADSCs have more effects by reducing aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at some time points and producing more liver-related growth factors, such as hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF). ADSCs have promising therapeutic effects for the treatment of ALF, there are limitations in terms of stem cell homing to target organs and poor transplantation efficiency. Lipid conjugated heparin coated ADSCs effectively alleviate these deficiencies and increase the therapeutic effects of ADSCs on liver diseases by enhancing ADSC homing to the liver and secretion of cytokines or growth factors. MSCs both BMSCs and ADSCs are promising therapeutic agents for the liver fibrosis and cirrhosis treatment because of their hepatic differentiation potential as well as their immunomodulatory properties and capacity to produce trophic factors. But there are still many problems to be addressed before clinical use of MSCs for liver

fibrosis/cirrhosis, including sufficient cell number, optimal time, and optimal delivery route for MSC transplantation. In this review, we suggest that formulating and following treatment guidelines is the most effective way to avoid treatment risks and improve treatment efficacy. Further studies are needed to determine the related mechanisms to enhance MSC efficacy in treatment of liver diseases especially fibrosis and Cirrhosis.

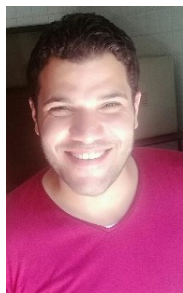
V. ACKNOWLEDGMENT

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