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EDITORIAL

# Are mesenchymal stem/stromal cells a novel avenue for the treatment of non-alcoholic fatty liver disease?

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## Abstract

In this editorial, we comment on the article by Jiang *et al*. Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease characterized by the accumulation of fat in the liver without evidence of significant alcohol consumption. NAFLD can progress to more serious conditions such as non-alcoholic steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. This disease is considered an emerging public health problem in several countries as it has increased in recent decades, currently affecting around 30% of the world's population. The fatty diet and the current lifestyle of the Western population are identified as the main culprits of the disease. Drug treatment aims to reduce the weight of patients and treat metabolic alterations and diseases, including type 2 diabetes mellitus and other comorbidities that coexist with NAFLD. In this scenario, cell therapy with mesenchymal stem/stromal cells (MSCs) has been proposed as a perspective treatment of numerous diseases that do not have definitive curative treatment, such as Crohn's disease and coronavirus disease 2019. This is due to the versatile, immunomodulatory and regenerative properties of MSCs. The possibility of MSCs being used in patients with severe liver disease progressing to non-alcoholic steatohepatitis or cirrhosis is summarized, because of the therapeutic benefits in reducing fibrosis of affected livers. It remains to be seen when MSC transplantation should be indicated for NAFLD, that is, at what stage of the disease and which phenotype, as well as deciding on the best source of MSCs, the dose, and the administration route. We conclude that well-designed clinical trials are essential in order to obtain robust results for the implementation of this modality in the medical practice.

**Key Words:** Non-alcoholic fatty liver disease; Mesenchymal stem/stromal cells; Stem cell therapy; Severe liver disease; Non-alcoholic steatohepatitis; Cirrhosis



**Core Tip:** As non-alcoholic fatty liver disease affects 30% of the world's population and it should be considered a public health problem. Mesenchymal stem/stromal cells (MSCs) are a type of cell with a high degree of differentiation, immunomodulatory and regenerative potential, which qualifies them for the treatment of inflammatory, autoimmune and immune-mediated diseases. MSCs could be the basis for developing drugs to treat diseases that currently have no definitive or curative treatment. MSCs have the potential to transform into hepatocytes and reduce steatosis and the degree of liver fibrosis. MSCs are promising for the treatment of non-alcoholic fatty liver disease, but there is a need to design clinical trials to obtain robust results for their implementation in medical practice.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease characterized by the accumulation of fat in the liver without evidence of significant alcohol consumption. NAFLD can progress to more severe conditions such as non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma[1,2]. Diagnosis of the disease begins with the clinical evaluation, followed by excluding viral causes, alcohol consumption and medications that cause liver damage. The gold standard for diagnosis is liver biopsy, and non-invasive imaging tests, such as ultrasound, proton magnetic resonance spectroscopy or quantitative fat-water magnetic resonance imaging. In addition to diagnosis, one objective of these techniques is to stage the disease and determine the severity of steatosis. NAFLD has different phenotypes and subtypes the definition of which depend on the prevalence, the patient's age and the percentage of hepatic steatosis. As a result of this evaluation, the disease can be called lean NAFLD or metabolically healthy NAFLD. Recently, the name metabolically dysfunction-associated fatty liver disease has been proposed when more than 5% of steatosis is associated with overweight/obesity, type 2 diabetes mellitus and evidence of metabolic dysregulation[3].

A systematic review to determine the prevalence of NAFLD and ultrasound-defined NAFLD demonstrated a global prevalence of 30.05% from 1990 to 2019. The prevalence of NAFLD increased by 50.4%, from 25.26% in the period from 1990-2006 to 38.00% between 2016 and 2019. The highest prevalence of NAFLD observed was in Latin America (44.37%), followed by the Middle East and North Africa (36.53%, 28.63%-45.22%), South Asia (33.83%), Southeast Asia (33.07%), North America (31.20%), East Asia (29.71%), Asia-Pacific (28.02%), and Western Europe (25.10%)[4]. The prevalence of metabolically dysfunction-associated fatty liver disease in the general population is estimated at 50.7% however this varies between the different countries analyzed[5]. In the United States, NAFLD is the most common cause of liver disease; NASH occurs in 20% of patients with NAFLD[5].

The most accepted etiology of NAFLD/NASH is a high-fat diet, that is, the Western pattern diet, which comes in different formulations, with various concentrations of fat and cholesterol, and can be administered with the addition of fructose[6]. The main cause of the evolution of NAFLD to NASH and, subsequently to cirrhosis when liver fibrosis occurs is inflammation and hepatocyte apoptosis[5,6]. The non-pharmacological treatment of NAFLD consists of changes in diet and lifestyle, as current pharmacological therapies focus on pathogenic factors and metabolic disorders. There is still a lack of specific medications for the disease. Among the medications that can be used for NAFLD are those that treat insulin resistance, type 2 diabetes mellitus, and dyslipidemia. Medications to reduce liver inflammation and fibrosis, such as vitamin E (alpha-tocopherol), obeticholic acid and pentoxifylline, can also be used. Currently, medications that cause weight loss, such as orlistat and glucagon-like peptide-1 receptor agonists (liraglutide, semaglutide), have gained ground in the treatment of patients with NAFLD. Other medications, such as elafibranor (a dual peroxisome proliferator-activated receptor α/δ agonist), cenicriviroc (a dual CC chemokine receptor 2 and CC chemokine receptor 5 antagonist, which can reduce inflammation and liver fibrosis) and aramchol (partial inhibitor of hepatic stearoyl-CoA desaturase, which may reduce liver fat), are also being studied[3,7].

Mesenchymal stromal/stem cells (MSCs) are considered a specific type of cells that can differentiate into various cell types, including osteoblasts, adipocytes, and chondrocytes. Found in the bone marrow, they can also be isolated from adipose tissue, umbilical cord, placenta, amniotic fluid, blood vessels and skeletal muscle. Due to their versatility and therapeutic potential, MSCs have been proposed for research and regenerative cell therapy. MSCs proliferate in culture without losing their differentiation properties and, when cultured *in vitro*, they present a fibroblastoid morphology[8].

MSCs have the ability to adhere to plastic and, *in vitro*, they express the CD105, CD73 and CD90 cell surface markers, and do not express CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR. This combination of behavior and marker expression is used to identify MSCs[9,10]. Due to their regenerative, immunomodulatory and anti-inflammatory

properties, MSCs can be used to treat patients with various conditions, such as musculoskeletal, cardiovascular, neurological, inflammatory and autoimmune diseases, as well as skin lesions and diseases.

MSCs have been used to control graft-*versus*-host disease (GvHD), a commonly observed event in allogeneic hematopoietic stem cell transplantation (allo-HSCT). In a study of 55 patients with acute and steroid-resistant GvHD, the use of bone marrow-derived MSCs provided a dramatic improvement in the clinical picture, demonstrating that an infusion of *in vitro* expanded cells, in addition to being beneficial, is an effective therapy for patients with GvHD after allo-HSCT[11,12]. Recent data also indicate that MSCs, in addition to controlling GvHD, maintain the graft-*versus*-leukemia effect longer, which is essential to control the disease in patients undergoing allo-HSCT[13].

MSCs modulate immune responses, maintain self-tolerance, and have immunosuppressive capabilities, making them ideal in the treatment of severe autoimmune and autoinflammatory diseases[14]. Thus, immune-mediated inflammatory diseases, such as Crohn's disease (CD), rheumatoid arthritis, multiple sclerosis, systemic sclerosis, lupus and many other serious and currently incurable diseases, can be targets for treatment with MSCs[15].

CD is an extremely serious and heterogeneous inflammatory bowel disease, which can affect the entire digestive system from the mouth to the anus. The disease progresses with gut dysbiosis of an autoimmune nature, which is responsible for the patients' symptoms. Stem cell transplantation and cell therapy can be valuable to provide long-term remissions in the treatment of critically ill patients refractory to conventional treatments[16-18]. Anal fistulas are frequent complications in CD patients; the direct application of MSCs to lesions has shown promising results, opening up the prospect of their routine and systemic use in patients with severe clinical events[19].

In 2019, the world was surprised by the severe acute respiratory syndrome coronavirus 2 pandemic, the virus responsible for coronavirus disease 2019, which claimed the lives of more than 7 million people according to data from the World Health Organization published in August 2023. Despite advances in vaccination, ideal for controlling the disease, the virus continues to circulate and cause mild to severe clinical conditions. In this context, MSCs are at the forefront as promising candidates, due to their immunomodulatory and regulatory capabilities of the innate and adaptive immune systems, release of anti-inflammatory biomolecules, suppression of inflammatory cytokine proliferation, direct cellular action and regeneration of tissues damaged by coronavirus disease 2019[20].

MSCs have facilitated the development of drugs for the treatment of autoimmune and inflammatory diseases. One successful example is darvadstrocel, a cell therapy drug that has been used worldwide to treat perianal fistulas in CD; it was one of the first cell therapies that passed from initial concept through clinical trials and care phases complying with the European Union regulatory guidelines[21]. At present, there are ten drugs derived from MSCs intended for the treatment of GvHD, CD fistulas, subcutaneous tissue disorders, amyotrophic lateral sclerosis, knee articular cartilage management, spinal cord injury, critical lower limb ischemia and acute myocardial infarction lesions[20].

## MSCS AND LIVER DISEASE

MSCs have demonstrated positive effects in various contexts related to liver disease, including degenerative and immune-related diseases. However, it remains uncertain whether MSC-based therapy is more effective than traditional treatments, and it is still unclear which specific types of liver diseases would benefit most from MSC therapy.

Liver cirrhosis, including viral, autoimmune, ischemic and alcoholic causes, is by far the most common application in clinical trials at about 68% of all research. This is followed by liver failure (about 20%) and complications after liver transplantation (about 11%). Although most clinical trials involving liver disease report promising results, not every clinical trial was positive. Of the 22 clinical trials completed in 2020, only three had negative results and another two had partial improvements or improvements that were not maintained.

Mohamadnejad *et al*[22] reported part improvements in a model for end-stage liver disease (MELD) but no change in liver regeneration or fibrosis six months after the transplant in a study of four patients with decompensated liver cirrhosis. In a second study by the same authors, 15 patients with decompensated liver cirrhosis showed no improvement in the Child and MELD scores, or liver function. The authors concluded that autologous bone marrow MSC transplantation through a peripheral vein probably has no beneficial effect in cirrhotic patients[23]. Detry *et al*[24] reported that an infusion of MSCs in ten patients who underwent liver transplantation was insufficient to allow withdrawal of immunosuppression compared to a control group. According to Peng *et al*[25] the short-term efficacy of an infusion of MSCs was favorable, but the long-term outcomes were not markedly improved. Their randomized controlled trial enrolled 53 patients with liver failure caused by hepatitis B in the study arm and 105 in the control group. Moreover, Kantarcıoğlu *et al*[26] reported in a study of 12 patients with liver cirrhosis partly improvement of MELD and no change in liver regeneration or fibrosis after six months.

## MSCS AND NAFLD

In this issue, Jiang *et al*[27] publish the article "Current perspectives on mesenchymal stem cells as a potential therapeutic strategy for non-alcoholic fatty liver disease". The importance of this topic was very well described and emphasized by the authors throughout the text. Below, we comment on some aspects of the challenges and the steps that we consider mandatory in order to implement MSC therapy in NAFLD and other liver diseases.

There is evidence that MSCs can differentiate into hepatocytes, which demonstrates their therapeutic potential in the treatment of liver diseases, due to their regenerative, anti-inflammatory and immunomodulatory properties, as previously described. Numerous studies investigating the potential of MSC-based therapy in the treatment of NAFLD

have consistently given promising results, such as improved liver function, reduced inflammation, and attenuated fibrosis in animal models and early clinical trials[27]. The mechanisms by which MSCs exert their beneficial effects in NAFLD are related to their ability to modulate the immune response, promote hepatocyte regeneration, and inhibit hepatic stellate cell activation. At this point, because of the evidence reported by several authors regarding the therapeutic potential in NAFLD, some questions arise regarding the ideal use of MSCs. Is this the moment, or do we still have a long way to go? For what type of patients? What phenotype of NAFLD can be treated? When should we indicate MSCs? In addition to the above, there are other questions and challenges that have not yet been answered and that need to be addressed: What is the best source of MSCs for the treatment of NAFLD? And the best administration route? How can the long-term safety and effectiveness of treatment be evaluated? And the main thing as we already mentioned is to identify the patients who can undergo treatment and who have the potential to respond, which could be, in our view, a way out for more seriously ill patients waiting for a possible liver transplant. Thus, the use of MSCs in the treatment of NAFLD is an emerging field of research with promising potential, but we must consider that it is still in the experimental phase. MSCs have immunomodulatory and regenerative properties that seem to be beneficial in the treatment of liver disease[27]. Below, we informatively summarize the potential benefits of MSCs in the treatment of NAFLD: (1) Anti-inflammatory properties: MSCs can reduce inflammation in the liver, an important feature of NASH, a more severe form of NAFLD; (2) Regenerative capacity: MSCs have the ability to differentiate into different cell types, including hepatocytes (liver cells), potentially helping in the regeneration of damaged liver tissue; and (3) Antifibrotic effects: MSCs can reduce liver fibrosis, a complication of NAFLD, by promoting tissue remodeling and reduced liver scarring. Among the studies, there is evidence that has been assessed in animal models in which the administration of MSCs reduces hepatic inflammation, fibrosis and improves liver function. Clinical trials are needed to evaluate the safety and efficacy of MSCs in treating liver diseases, including NAFLD. Preliminary preclinical results are promising, but more research is needed to confirm its efficacy and safety.

The mechanisms of action of MSCs and their therapeutic effects can occur through several mechanisms: (1) Immune modulation: MSCs can suppress abnormal inflammatory response and regulate the immune system, reducing inflammation in the liver; (2) Release of growth factors: MSCs secrete growth factors that promote cell regeneration and liver tissue repair; and (3) Interaction with liver cells: MSCs can directly interact with liver cells to promote regeneration and reduce apoptosis (cell death). Finally, there is the cost of treatment with MSCs, which can be expensive, a fact that could result in limitations and accessibility for many patients[28].

### *Limitations*

While MSC therapies hold great promise, they still face several limitations. The lack of standardization in the isolation, culturing, and administration of MSCs is a significant challenge, as there is currently no universal protocol for these processes. This variability can lead to inconsistent results, complicating the development and application of therapies. Additionally, while MSCs have demonstrated therapeutic potential, the mechanisms behind their effects are not yet fully understood. A deeper understanding of how MSCs work could lead to more targeted and effective therapies. Safety is another concern, as, although MSC therapies are generally considered safe, they carry potential risks, in particular, long-term safety data remains limited, making it difficult to fully assess the risks over extended periods. Cost and accessibility are also barriers to the widespread use of MSC therapies. These treatments can be expensive, limiting access for many patients who could benefit from them. Finally, the variability in patient responses to MSC therapy presents a further challenge, as it is difficult to predict the outcomes for individual patients, complicating treatment planning. Despite these limitations, ongoing research and clinical trials are continuously advancing the field of MSC therapy.

### *Safety profile*

MSC therapy has shown promise in various clinical applications, but like any treatment, it carries potential risks and side effects that need to be considered. Common minor side effects include fever, local pain at the injection site, sleeplessness, and constipation. These side effects are generally temporary and tend to resolve on their own without significant intervention. Although rare, there have been reports of hemocompatibility issues with MSC therapy. Thromboembolic complications can occur when MSC products express high levels of tissue factor (CD142).

Long-term side effects of MSC therapy are still being studied. There is a potential risk of tumor formation due to the proliferative nature of stem cells, as well as immune reactions that could cause the body to reject the treatment. Furthermore, therapy failure is a possibility, where the desired therapeutic effects are not achieved. While MSC therapeutics have been safely administered in well-controlled clinical trials, it is important to note that many trials lack updates on their status or long-term follow-up data.

## CONCLUSION

The use of mesenchymal stem cells for the treatment of NAFLD is a promising area of research that may offer new therapeutic options for this disease. However, further investigations are essential through well-designed clinical trials, with the selection of patients with clinically well-defined phenotypes, to confirm the efficacy and safety of this approach before broader recommendations can be made in the clinical practice. Patients interested in this type of treatment should consider participating in clinical trials and discuss this possibility with their doctors.

## FOOTNOTES

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