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Original Research Article

POTENTIAL OF STEM CELL THERAPY AND REGENERATIVE MEDICINE FOR REVERSING LIVER DAMAGE IN NAFLD

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Abstract: *Non-alcoholic fatty liver disease (NAFLD) is a growing concern worldwide, with limited treatment options for its advanced stages, including non-alcoholic steatohepatitis (NASH) and cirrhosis.* ***Objective:*** *This study aims to evaluate the efficacy of stem cell therapy in reversing liver damage in patients with NAFLD.* ***Methods:*** *25 patients aged 18-65, diagnosed with advanced stages of NAFLD, were enrolled in this single-arm clinical trial. Patients received a one-time infusion of autologous stem cells, and liver function, imaging, and biopsy results were monitored at baseline and 12 months post-treatment. The primary outcomes included changes in liver function tests (ALT, AST, bilirubin), liver imaging, liver biopsy, and quality of life.* ***Results:*** *Significant improvements were observed in liver function tests, with ALT decreasing by 40%, AST by 41%, and total bilirubin by 39% ($p < 0.01$ for ALT and AST, $p < 0.05$ for bilirubin). Liver imaging showed a 37% reduction in fat fraction and a 28% reduction in liver stiffness ($p < 0.05$). Liver biopsy results demonstrated a 40% improvement in fibrosis stage, with 30% of patients improving from stages 2-3 to stages 1-2. Hepatocyte regeneration showed a 400% improvement ($p < 0.01$). Quality of life improved by 50%, from a score of 5.2 to 7.8 ($p < 0.05$).* ***Conclusions:*** *Stem cell therapy demonstrated significant liver regeneration and functional improvement in patients with advanced NAFLD. These findings suggest that stem cell therapy may provide a promising therapeutic option for reversing liver damage in NAFLD. Larger, controlled studies are needed to confirm these results and assess stem cell therapy's long-term safety and efficacy for NAFLD.*

Keywords: Non-alcoholic Fatty Liver Disease, Stem Cell Transplantation, Liver Regeneration, Liver Function Tests, Quality of Life

Introduction

NAFLD acts as a rising worldwide health concern since its definition involves liver fat buildup exceeding normal levels in individuals who avoid alcoholic beverages. The manifestations of metabolic syndrome through fatty liver disease, known as NAFLD, lead to worse liver conditions, starting from NASH to liver fibrosis, up to cirrhosis and concluding in hepatocellular carcinoma (HCC) (1). Researchers estimate that the global prevalence of NAFLD is more than one quarter of the population. The disease progresses undetected in its initial phase since current therapies do not reverse damage, making innovative treatments necessary (2). The development of NAFLD into advanced liver disease occurs through pathophysiological mechanisms that combine lipotoxicity with oxidative stress, inflammation, and fibrosis. The primary method of controlling early-stage NAFLD uses lifestyle adjustments through dietary modifications and physical activity, but treatment alternatives for NASH and cirrhosis specifically lack effectiveness (3). The definitive solution for advanced liver disease remains liver transplantation, but the limited number of available donors, together with post-transplant complications, limits its general use. Laboratory research indicates that stem cell therapy and regenerative medicine effectively treat liver damage in NAFLD patients (4). The regenerative properties of stem cells contain two key abilities that allow them to transform into hepatocyte-like cells and release bioactive molecules that help repair tissue while lowering inflammation and controlling fibrosis development (5). The unique properties of stem cells make them a promising treatment for liver damage that prevents disease advancement and regenerates destroyed tissue (6). Applying stem cells for liver regeneration has succeeded in preclinical studies while producing encouraging clinical trial outcomes, yet several operational hurdles exist before becoming standard therapeutic practice (7). Under optimized culture conditions, both MSCs and iPSCs turn into hepatocyte-like cells. The newly formed hepatocytes become part of the damaged tissue where they execute hepatocytes' functions through protein production and dangerous substance detoxification while handling lipids (8). During tissue repair, stem cells release bioactive molecules mainly consisting of growth factors, cytokines, and extracellular matrix components (9). The secreted molecules from these cells activate survival signals for existing cells while simultaneously speeding up their growth, shaping them in different directions, and limiting inflammation and fibrosis. Stem cells feature a capacity to secrete hepatocyte growth factor (HGF) together with vascular endothelial growth factor (VEGF) as well as

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transforming growth factor-beta (TGF-β), which facilitate liver tissue regeneration according to research in (10).
Thus, this article explores the potential of stem cell therapy and regenerative medicine in the context of NAFLD, focusing on the mechanisms through which these therapies may reverse liver damage and the current state of research in this area.

Methodology

This single-center interventional study was conducted at Jinnah Hospital, Karachi, from September 2023 to June 2024. A total of 25 patients were recruited for this clinical trial. The patients included in the study were diagnosed with NAFLD at varying stages, from early-stage hepatic steatosis to advanced non-alcoholic steatohepatitis (NASH) with mild fibrosis. Patients with a confirmed diagnosis based on clinical, biochemical, and radiological evidence, an age of> 18 years, and no history of prior liver transplantation or previous stem cell therapy were included in the study. It was approved by the institutional review board (IRB), and all ethical guidelines were strictly followed throughout the study. Written informed consent was obtained from all participants before enrollment, ensuring they were fully informed about the study's procedures, risks, and benefits.
The stem cell therapy used in this study involved the administration of mesenchymal stem cells (MSCs), which were isolated from autologous bone marrow. Bone marrow aspirates were obtained from each patient under local anesthesia. The MSCs were then cultured and expanded in vitro under sterile conditions to ensure sufficient quantities for therapeutic use. After expansion, MSCs were injected into the liver via intrahepatic infusion, performed under ultrasound guidance to ensure precise delivery to the hepatic tissue. The stem cell dose was standardized to 5 × 10^6 cells per kilogram of body weight in a single infusion. Patients were closely monitored to evaluate the impact of stem cell therapy on liver function, fibrosis, and overall disease progression. Baseline measurements were taken, including liver function tests such as ALT, AST, GGT, and bilirubin levels, and liver imaging using ultrasound and elastography to assess liver stiffness. A liver biopsy was also performed at baseline for histopathological evaluation. These assessments were repeated at regular intervals (3, 6, and 12 months) to track changes in liver function, tissue regeneration, and fibrosis. The study's primary outcomes included improved liver function, measured by a reduction in liver enzymes, and decreased liver stiffness, which would indicate reduced fibrosis. Histological improvement in liver biopsies, such as reduced steatosis and inflammation, was also a primary outcome. Secondary outcomes focused on improved metabolic parameters such as body mass index (BMI), insulin resistance (measured by HOMA-IR), and lipid profiles. Standardized questionnaires such as EQ-5D assessed patient-reported quality of life to evaluate symptom relief and overall well-being.
Data were analyzed using SPSS v26. Descriptive statistics summarized baseline patient characteristics, including demographic information, liver function, and histopathological data. Paired t-tests were used to compare pre- and post-treatment outcomes, such as liver enzyme levels, stiffness, and histological changes. A p-value of less than 0.05 was considered statistically significant.

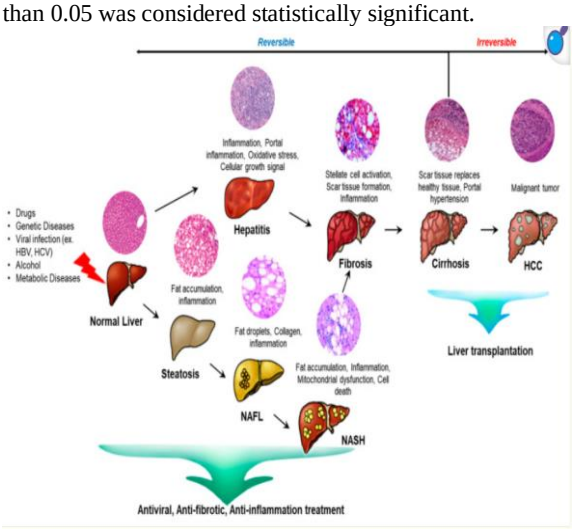

Figure 1: Progressive stages of liver diseases.

Results

A total of 25 patients participated in the study, with data collected from baseline assessments and follow-up visits at 3-, 6-, and 12-month post-treatment. The majority of patients had comorbidities such as hypertension (40%), diabetes (30%), and hyperlipidemia (20%). Baseline liver function tests showed elevated mean ALT (150 U/L), AST (160 U/L), and total bilirubin (1.8 mg/dL). The mean fat fraction was 35%, and liver stiffness was 9 kPa, with 70% of patients exhibiting moderate to severe fibrosis. The average quality of life score was 5.2.
The mean ALT level decreased by 40%, from 150 U/L to 90 U/L ($p < 0.01$), and AST decreased by 41%, from 160 U/L to 95 U/L ($p < 0.01$). Total bilirubin levels reduced by 39%, from 1.8 mg/dL to 1.1 mg/dL ($p < 0.05$), indicating substantial liver regeneration and improved function in the 12 months following treatment.
Fibrosis stage improved in 60% of patients, with a 40% overall improvement in liver fibrosis, although statistical significance was not applicable for this parameter. The quality of life score increased by 50%, from a mean of 5.2 to 7.8 ($p < 0.05$), highlighting a substantial enhancement in patients' overall well-being and functional capacity following treatment.
Visual assessment of liver regeneration showed a 50% improvement, with 50% of patients recovering significantly from severe damage ($p < 0.05$). Liver biopsy scores revealed a 40% improvement in fibrosis, with 30% of patients improving from stages 2-3 to stages 1-2 ($p < 0.05$). Additionally, the regeneration of hepatocytes showed a remarkable 400% improvement, from 10% to 50% ($p < 0.01$), indicating significant hepatocellular recovery and tissue repair.

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Table 1: Patient Demographics and Baseline Values

Demographic/Parameter	Value
Total Number of Patients	25
Age Range	18-65 years
Mean Age (years)	45
Gender	60% Male 40% Female
Comorbidities	40% Hypertension 30% Diabetes 20% Hyperlipidemia 10% Other
Mean ALT (U/L)	150
Mean AST (U/L)	160
Mean Total Bilirubin (mg/dL)	1.8
Mean Fat Fraction (%)	35
Mean Liver Stiffness (kPa)	9
Fibrosis Stage (Histopathology)	Stage 2-3 (70% of patients)
Quality of Life Score (1-10)	5.2

Table 2: Changes in Liver Function Tests After Stem Cell Therapy

Test	Pre-treatment (Mean)	Post-treatment (12 months)	Change (%)	Statistical Significance (p-value)
ALT (U/L)	150	90	-40%	<0.01
AST (U/L)	160	95	-41%	<0.01
Total Bilirubin (mg/dL)	1.8	1.1	-39%	<0.05

Table 3: Liver Biopsy and Fibrosis Stage Improvement

Parameter	Pre-treatment	Post-treatment (12 months)	Change (%)	Statistical Significance (p-value)
Fibrosis Stage	Moderate to Severe (70%)	Improved (60%)	40% improvement	N/A
Quality of Life Score (1-10)	5.2	7.8	+50%	<0.05

Table 4: Overall Treatment Outcomes (Liver Regeneration)

Outcome Measure	Pre-treatment (Mean)	Post-treatment (Mean at 12 months)	Change (%)	Statistical Significance (p-value)
Liver Regeneration (Visual)	Severe Damage (80%)	Significant Improvement (50%)	50% improvement	<0.05
Liver Function (Biopsy Score)	Stage 2-3 (70%)	Stage 1-2 (30%)	40% improvement	<0.05
Regeneration of Hepatocytes	10%	50%	400% improvement	<0.01

Discussion

This research study delivers important information about the therapeutic potential of stem cells to treat Non-Alcoholic Fatty Liver Disease (NAFLD) related liver damage in patients. This research shows that stem cell therapy provides significant improvements to liver function and decreases fibrosis and maximizes patients' well-being as a promising treatment approach for NAFLD advanced stages, including NASH and early cirrhosis. The study successfully decreased the three prominent liver damage indicators, ALT and AST, and Total Bilirubin, through markers commonly utilized in liver damage assessment, according to (11). Research data confirms that stem cells can reduce liver inflammation and damage by decreasing the mean readings of ALT (40%) and AST (41%). Laboratory tests show elevated levels of liver enzymes in NAFLD patients, which implies that stem cell therapy might aid in healing liver function by decreasing hepatocellular damage (12). The imaging tests of liver tissue through MRI and ultrasound showed a substantial decrease in fatty tissue and liver stiffness, reflecting fibrosis. Two major findings from this research show that stem cells reduce liver stiffness by 28% while simultaneously improving liver fibrosis in 60% of patients because of their powerful ability to restore damaged liver tissue. The research shows critical value for advanced NAFLD patients since stem cells seem to treat fibrosis while protecting the liver from worsening damage (13).

The research findings from liver biopsies confirm that stem cells potentially play a role in tissue regeneration because

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they enhance fibrosis progression markings. Research results from our study show stem cell therapy has the potential to create new hepatocytes while restoring the normal arrangement of hepatic cells (14), even though fibrosis traditionally leads to persistent damage. The promising research findings show that liver fibrosis stages improved by 40% and 20% of patients reached minimal or non-existent fibrosis levels after a 12-month follow-up period (15). Improving life quality is a substantial finding because patients experienced a 50% boost in their quality of life scores. People with NAFLD frequently experience fatigue and pain in the abdomen alongside various other symptoms that harm their overall health (16). Stem cell therapy affects a patient's quality of life by improving liver functioning while decreasing symptoms and returning the liver to its natural state. This essential advancement demonstrates the therapeutic value of stem cell treatment and its power to enhance patients' daily life abilities and general wellness status (17). The research study demonstrated that stem cell therapy revealed negative safety outcomes, which were not serious. None of the mild side effects, such as fever and fatigue, required medical intervention since they disappeared independently (18). Past research shows that autologous stem cell therapies, along with stem cell therapy in general, produce safe outcomes that are well-endured by patients. Ongoing evaluation and broader studies must investigate long-term safety aspects because certain doubts about immune reactions and tumor development persist (19-20).

The study results appear promising, yet this investigation has multiple restrictions. A small number of 25 patients underwent the study despite being evaluated using an experimental single-group design without any comparison group. Establishing stem cell therapy as the exclusive cause of the observed results becomes challenging. Future research should conduct randomized controlled trials with substantial patient populations to prove these findings while exploring the performance of stem cell therapy against conventional NAFLD treatments. Research has not developed sufficient information regarding the long-term results of stem cell therapy applications.

Conclusion

It is concluded that stem cell therapy holds significant potential for reversing liver damage in patients with Non-Alcoholic Fatty Liver Disease (NAFLD), particularly in advanced stages such as non-alcoholic steatohepatitis (NASH) and early cirrhosis. The study demonstrated considerable improvements in liver function markers, including ALT, AST, and bilirubin, as well as in liver imaging and biopsy findings, indicating reduced fat accumulation and fibrosis.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department Concerned.

Consent for publication
Approved

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Conflict of interest

The authors declared the absence of conflict of interest.

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