
QUANTUM STEM CELL THERAPY FOR RECOVERY OF LIVER DISEASE

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ABSTRACT

Chronic liver diseases pose a significant global health challenge, necessitating the development of novel therapeutic strategies for liver regeneration and functional recovery. Mesenchymal stem cells (MSCs) derived from umbilical cord blood have emerged as promising candidates for liver regeneration due to their multipotent differentiation capacity, immunomodulatory properties, and paracrine effects. This study aims to investigate the efficacy, safety, and underlying mechanisms of stem cell therapy in the recovery and regeneration of liver tissue in patients with liver disease. The research method used is a case study where Mesenchymal Stem Cell therapy offers the potential to modify the natural recovery of Liver function using stem cell-based technology. Case studies were carried out on several Vinski Regenerative Center clinic patients. This review explores the therapeutic potential of umbilical cord blood-derived MSCs in promoting the recovery of liver function in preclinical and clinical settings. We discuss the mechanisms by which MSCs facilitate liver regeneration, including their ability to differentiate into hepatocyte-like cells, modulate immune responses, and secrete trophic factors that promote tissue repair. Preclinical studies demonstrate the efficacy of umbilical cord blood-derived MSCs in ameliorating liver injury, reducing fibrosis, and improving overall liver function. Challenges such as optimal dosing, timing of administration, and long-term monitoring remain to be addressed. Nevertheless, MSCs from umbilical cord blood represent a promising therapeutic approach for liver regeneration and hold great potential for improving outcomes in patients with liver disease.

Keywords: Stem Cell, Liver Disease, Regenerative Medicine, Cell Therapy, Mesenchymal Stem Cell, Human Liver Liver Stem Cell.

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INTRODUCTION

Chronic liver diseases, including cirrhosis, hepatitis, and nonalcoholic fatty liver disease, represent a significant global health burden, affecting millions of people worldwide (Asrani et al., 2019). Despite advances in medical treatment, liver transplantation remains the definitive therapy for end-stage liver disease. However, organ shortage, surgical complications, and the need for lifelong immunosuppression limit transplantation's widespread availability and efficacy (Khalil et al., 2023).

In recent years, regenerative medicine approaches utilizing stem cells have emerged as promising therapeutic strategies for liver regeneration and functional recovery. Among these, mesenchymal stem cells (MSCs) derived from various sources, including bone marrow, adipose

tissue, and umbilical cord blood, have garnered considerable attention due to their multipotent differentiation capacity, immunomodulatory properties, and paracrine effects (Han et al., 2019); (Nazarian et al., 2021).

This study investigates the potential of MSCs derived from umbilical cord blood to promote liver function recovery in preclinical and clinical settings. Specifically, it aims to evaluate the therapeutic efficacy, safety profile, and mechanisms of action underlying MSC-based therapies in liver regeneration and repair.

This research contributes to the growing body of knowledge on stem cell-based therapies for liver diseases by providing insights into the regenerative potential of MSCs derived from umbilical cord blood. By elucidating the mechanisms by which MSCs promote liver regeneration, the study seeks to inform the development of novel therapeutic interventions to improve clinical outcomes for patients with liver disease.

Furthermore, this research has translational implications for developing MSC-based regenerative therapies that could reduce the need for liver transplantation and offer alternative treatment options for patients with advanced liver disease. Additionally, by exploring the safety and feasibility of MSC transplantation in clinical trials, this study aims to pave the way for the broader adoption of stem cell-based therapies in managing liver diseases, addressing unmet medical needs and improving patient quality of life.

Research into stem cell therapy for liver disease is a rapidly evolving field with significant potential. However, there are several gaps and challenges that need to be addressed to advance this therapy effectively. Mechanisms of Action like how to understanding Mechanisms : More research is needed to fully understand the mechanisms through which stem cells contribute to liver regeneration. This includes their interaction with the liver microenvironment, immune modulation, and differentiation into hepatocytes. Long-Term Effects Long-term effects and integration of stem cells in the liver tissue are not well understood. Addressing these gaps through coordinated research efforts, interdisciplinary collaboration, and robust clinical trials will be essential to realize the full potential of stem cell therapy for liver disease recovery.

However, there are several gaps and challenges that need to be overcome for this therapy to work effectively starting from the Mechanism of Action such as how to understand the Mechanism. More research is needed to fully understand the mechanisms through which stem cells contribute to liver regeneration. The long-term effects and integration of stem cells in liver tissue are not well understood. Addressing these gaps through coordinated research efforts, interdisciplinary collaboration, and robust clinical trials will be critical to realizing the full potential of stem cell therapy for liver disease recovery. This study reviews the potential of mesenchymal stem cells (MSCs) for liver regeneration, highlighting their immunomodulatory properties and ability to differentiate into hepatocyte-like cells.

Causes of Liver Disease

Viral Infections

Hepatitis A is an RNA virus belonging to the Picornaviridae family. It is present in the highest concentration in the stool of infected persons, where the most significant release of the viral load is at the end of the incubation period. Hepatitis A is most often transmitted through the faecal-oral route from contact with water, food, or objects contaminated with the faeces of an infected person (Koenig et al., 2017). Primarily, the hepatitis A virus replicates in hepatocytes. At the same time,

animal studies suggest possible replication in epithelial cells of tubular crypts and lamina propria cells. After ingestion, the virus from the gastrointestinal tract will take over, and its particles are transported to the basolateral membrane of hepatocytes via the portal circulation. In acute hepatitis A infection, hepatocellular injury is mediated by various immunological mechanisms. Patients with acute infection with hepatitis A virus have a specific release of cytotoxic interferon-gamma that is virus-specific and mediated by T cells. After replicating in the, the hepatitis A virus is secreted through the gums and released in the stool (Iorio & John, 2023).

Hepatitis B virus is a DNA virus that belongs to the Hepadnaviridae family. The viral core consists of the nucleocapsid, hepatitis B core antigen (HBcAg), which surrounds the viral DNA and DNA polymerase (Mehta & Reddivari, 2021). The hepatitis B surface antigen (HBsAg) is coated on the nucleocapsid. HBsAg is a surface polypeptide. The gene that codes for HBcAg also codes for hepatitis B e antigen (HBeAg). Hepatitis B virus has eight genotype variants (You et al., 2014). Hepatitis B virus is transmitted by mucosal exposure to infectious body fluids or percutaneous inoculation. Although very rare, oral-fecal transmission is possible. The incubation period of the hepatitis B virus is between 30 and 180 days. HBsAg is transmitted through contact with body fluids or blood. At the same time, the risk of infection is higher in people in close contact with HBsAg positive. The pathogenesis of liver disease in hepatitis B virus infection is immunologically mediated. Sometimes, the infection can cause direct cytotoxic liver injury (Chisari et al., 2010).

HBsAg and other nucleocapsid proteins on cell membranes promote T cell-induced lysis of hepatitis B virus-infected cells. The cytotoxic response of T cells to hepatitis B virus-infected hepatocytes is relatively ineffective. In contrast, most hepatitis B virus DNA is cleared from the liver system before maximal infiltration of T cells. This indicates that the immune response is more robust in the early phases of the virus infection. However, the immune response is potentially not the only aetiology of liver injury in patients infected with the hepatitis B virus. Injuries associated with hepatitis B virus have also been observed in patients with hepatitis B virus after liver transplantation who adhere to immunosuppressive therapy. The histological pattern of infection in patients after liver transplantation is called fibrosing cholestatic hepatitis and is thought to be associated with high HBsAg expression, suggesting that the hepatitis B virus may be pathogenic regardless of the immune response (Chisari et al., 2010).

Hepatitis C is an RNA virus belonging to the Flaviviridae family with one serotype, at least six major genotypes, and more than 80 subtypes (Mehta & Reddivari, 2021). It is most often transmitted through the sharing of infected needles among people who use IV drugs. It can also be transmitted parentally, perinatally, and sexually. Other people at high risk of hepatitis C are people who frequently need blood transfusions or organ transplants from an infected donor (Li & Lo, 2015).

Hepatitis C virus enters hepatocytes through endocytosis, which is mediated by at least four receptor molecules. After internalization in the cytoplasm, the positive-stranded RNA is unlabeled and translated into ten mature peptides. Peptides are then cleaved with the help of host proteases and virally encoded proteases (NS3-4a serine proteases). Mature peptides reside on the endoplasmic reticulum, where a replication complex is formed that contains the enzyme NS5B RNA-dependent RNA polymerase, which catalyzes the positive RNA chain into its negative chain intermediate, which serves as a template for the synthesis of a new RNA positive chain. Next, the new positive RNA is packaged with the core and enveloped glycoprotein into mature virions that exit the cell via exocytosis. The hepatitis C virus can integrate into the host's genome. Persistent hepatitis C virus

infection is thought to occur due to weak CD8+ and CD4+ T cell responses, which cannot control viral replication. After the establishment of chronic hepatitis C virus infection, it is no longer a cytopathic but a local inflammatory response that triggers fibrogenesis. Accelerated progression of fibrosis and cirrhosis are associated with various external factors, including coinfection with HIV or hepatitis B, alcohol consumption, obesity, insulin resistance, nonalcoholic fatty liver disease, etc.

The Hepatitis D virus is an RNA virus belonging to the genus Deltavirus (Mehta & Reddivari, 2021). It consists of the hepatitis D antigen (HDAg), RNA genome, and lipoprotein envelope of the hepatitis B virus. The hepatitis D virus genome encodes only HDAg. Replication takes place in hepatocytes. The Hepatitis D virus is unique because it uses the host's RNA polymerase II to transcribe its messenger RNA (mRNA). There are two HDAgs, i.e. long and short. Short HDAg activates viral replication through direct binding to hepatitis D virus RNA.

In contrast, long HDAg directs viral assembly and inhibits viral replication. The virus is fully assembled after incorporating the herpesvirus B envelope, after which the virus is released (Ni et al., 2014). Hepatitis D virus infection occurs only when hepatitis B virus is present. Coinfection of hepatitis B and D in persons susceptible to hepatitis B virus infection leads to acute infection. Coinfection clinically resembles acute hepatitis B, except that a biphasic course of two levels of serum alanine aminotransferase (ALT) can be observed a few weeks apart. This happens because hepatitis B infection must first be established during acute coinfection before the spread of the hepatitis D virus begins (Masood & John, 2017).

Hepatitis E is an RNA virus that belongs to the genus Hepevirus. The fecal-oral route is the primary way of transmission, and it can also be transmitted through fecally contaminated water. Person-to-person transmission is rare, while mother-to-newborn transmission has occasionally been reported (Pérez-Gracia et al., 2015). The Hepatitis E virus targets hepatocytes, and it is thought that the virus replicates enterally because ORF2 antigens and RNA of the hepatitis E virus have been found in the intestinal crypts of chronically infected patients. It is believed that the hepatitis E virus enters the portal circulation and infects hepatocytes, leading to inflammation. However, the mechanism of hepatitis E virus entry into hepatocytes is not fully understood (Iqbal et al., 2023). After the virus enters the hepatocyte, the hepatitis E virus genome is released in the cytoplasm, and the virus hijacks the intracellular machinery for the replication of viral proteins and the RNA genome. ORF4 is essential for replication, while ORF3 is necessary for virus release from infected cells. The combination of human immune response and cellular immunity limits viral replication, allowing the host to clear the infection. Anti-hepatitis E virus immunoglobulin M (IgM) antibodies in acutely infected patients reach their maximum at six weeks, followed by anti-hepatitis E virus IgG antibodies for long-term protection lasting years to decades. Acute hepatitis E virus infection is associated with elevated T cells, increased CD8+ and CD4+ cells, and additional release of the anti-inflammatory and pro-inflammatory cytokines interferon-gamma (IFN-gamma) and interleukin 10 (IL-10). Further immunological protection is provided by the innate response of lymphoid cells with natural killer cells that fight cell-mediated cytotoxicity IFN-gamma production and viral infection. The immune response that is responsible for organizing hepatitis E virus infection is also the cause of hepatocellular damage and liver inflammation (Iqbal et al., 2023).

The Hepatitis G virus is an RNA virus belonging to the Flaviviridae family. Primarily, the virus is transmitted through infected blood and blood products. Hepatitis G virus infection usually occurs as a coinfection with chronic hepatitis C or hepatitis B. Although the hepatitis G virus is associated with

chronic liver disease, it has not been established that it causes hepatitis by itself (Soleiman-Meigooni et al., 2015). In addition to hepatitis virus, other viruses such as Varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus (Mehta & Reddivari, 2021) can cause hepatitis or liver diseases such as Dengue virus, Hantavirus, yellow fever virus, Lassa virus, Junin virus, Chikungunya virus, Congo-Crimea Hemorrhagic fever virus, Rift Valley fever virus, Marburg virus, Adenoviruses and Ebola virus (Spengler, 2020).

An Autoimmune Disease That Causes the Body's Immune System to Attack Healthy Cells or Tissue in the Liver – Autoimmune Hepatitis

Autoimmune hepatitis is a condition in which cells of the immune system attack and destroy liver cells. The etiology of autoimmune hepatitis is still unknown. Pathogenesis is thought to be secondary to the failure of immunological tolerance in genetically susceptible individuals, which leads to T-cell-mediated inflammation caused by various environmental triggers. Toxins, drugs, or infections usually trigger autoimmune hepatitis. Specific human leukocyte antigen (HLA) haplotypes are more susceptible to developing autoimmune hepatitis. In different ethnic groups, there are different susceptible alleles. In Northern Europeans and North Americans, susceptible alleles are located on the short arm of chromosome 6, that is, the DRB-1 region. Autoimmune hepatitis has been associated with tumour necrosis factor-alpha. At the same time, minocycline and nitrofurantoin (Linzay et al., 2021), methyldopa, infliximab, adalimumab, and minocycline have been documented as drugs causing autoimmune hepatitis (Linzay et al., 2021); (Mehta & Reddivari, 2021). However, after stopping treatment with drugs that cause autoimmune hepatitis, the disease improves (Mehta & Reddivari, 2021).

Genetic Factors

Liver diseases caused by gene mutations are defined as monogenic liver diseases or hereditary liver diseases. They mostly have overlapping phenotypes and lack specific laboratory test indicators (Fang et al., 2021). Genetic causes lead to a wide range of liver function disorders, including alpha-1 antitrypsin deficiency, Wilson's disease, Gilbert's syndrome, hemochromatosis, Lysosomal acid lipase deficiency (LAL-D), progressive familial intrahepatic cholestasis (PFIC), and benign recurrent intrahepatic cholestasis (BRIC). The C252Y mutation in the HFE gene is the most common cause of hereditary chromatinosis. Alpha-1 antitrypsin deficiency is an autosomal recessive disease that can cause liver disease (elevated bilirubin and transaminases, or/and liver cirrhosis) and panacinar emphysema. Wilson's disease is caused by possessing an autosomal recessive mutation of the ATP7B gene, which leads to the accumulation of copper in the liver, brain, cornea, and kidneys, which can manifest as various diseases. PFIC occurs due to PFIC3, PFIC2, and PFIC1 mutation, leading to chronic cholestasis. BRIC also occurs due to a PFIC gene mutation, with the disease occurring as episodes of cholestasis (Schonfeld & Brown, 2019). New sequencing technologies have contributed significantly to understanding the genetics of liver disease and have already led to new treatments, diagnostic methods, management, etc. (Konkwo et al., 2024).

The Habit of Consuming Excessive Alcoholic Drinks

Alcoholic liver disease includes several liver disorders, including fatty liver that can progress to alcoholic hepatitis and alcoholic liver cirrhosis, which is the most irreversible and advanced form of alcohol-related liver damage. The three histological stages of alcoholic liver disease are steatosis or alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. In the stage of steatosis, mass accumulates in the liver parenchyma. Then, as the disease progresses to alcoholic hepatitis, liver cell

inflammation occurs, where the outcome depends on the severity of the damage. Alcoholic hepatitis can be treated with alcohol abstinence, infection treatment, nutritional support, and prednisolone therapy. However, in severe cases, alcoholic liver hepatitis leads to liver failure. Alcoholic cirrhosis represents liver damage that is irreversible and leads to complications of cirrhosis and portal hypertension (Patel et al., 2021).

Unhealthy Eating Patterns

Diet is one of the environmental factors that influence the development of nonalcoholic fatty liver disease (NAFLD). An increased intake of red meat is associated with a higher risk of NAFLD. In contrast, a reduced risk is associated with the intake of fruits, cereals, and tea, as well as with the development of cirrhosis and liver cancer (Guo et al., 2022). Increased poultry meat intake and reduced cheese intake are also associated with an increased risk of NAFLD (Guo et al., 2022).

Obesity

Obesity is a known risk factor for liver injury, including NAFLD. It may be caused by excessive fat accumulation, leading to excessive hepatic fatty acid supply, liver injury, and chronic low-grade inflammation (Luo & Lin, 2021). The body mass index is used as a group of measures of general obesity. However, waist circumference is a better index of abdominal obesity and is strongly associated with abdominal fat distribution. Abdominal obesity and general obesity have been suggested to be a risk factor for liver injury. General obesity has a more significant influence on the association with liver enzyme levels and the prevalence of abnormal liver enzymes than abdominal obesity (Huang et al., 2023).

Drug Abuse

Drug-induced hepatotoxicity is a chronic or acute liver injury that occurs as a result of the consumption of drugs or herbal compounds. More than 1000 drugs and herbal compounds cause hepatotoxicity. Drug-induced liver injury can be intrusive and idiosyncratic (Francis & Navarro, 2020). After cannabis, the second and third most commonly abused drugs are opioids and cocaine. Although opioids are generally not involved in a large number of cases of acute liver injury, they do lead to liver injury. However, cocaine affects the liver by causing liver necrosis, while liver enzymes change only after two days of use. Damage to the liver by cocaine is accompanied by damage to other organs, such as kidney failure, myocardial infarction, and rhabdomyolysis. Cocaine leads to necrosis of the liver, where there is a markedly higher level of aminotransferase and lactate dehydrogenase with a minimal increase in alkaline phosphatase. After acute liver injury, bilirubin increases two to three days later than liver enzymes. In some instances, recovery is self-limited when liver enzymes decrease over two weeks (Dolkar et al., 2022)

Exposure to Toxic Chemical Compounds

Environmental and occupational exposure to industrial chemicals can lead to liver damage and hepatotoxicity in humans and animals (Lang & Beier, 2018). Compounds that have been shown to cause liver injury include leachable organic substances (Lang & Beier, 2018), perfluorinated alkyl substances (Sen et al., 2022), organic solutions (dimethylformamide, dimethylacetamide, trichloroethylene, tetrachloroethylene, carbon tetrachloride, xylene, toluene, and chloroform; (Malaguarnera et al., 2012), vinyl chloride, toxic oil syndrome, aflatoxins, anilines (Wahlang et al., 2013), chemical compounds in cigarette smoke (Barouki et al., 2023), etc.

Cancer Cell Growth

Hepatocellular liver cancer is the primary cancer with the highest prevalence of liver cancer. So far, several histological subtypes of hepatocellular carcinoma of the liver are known, including CAP carcinoma, transitional liver cell tumour, steatohepatic hepatocellular carcinoma, diffuse cirrhosis-like hepatocellular carcinoma, clear cell hepatocellular carcinoma, sarcomatoid hepatocellular carcinoma, combined hepatocellular carcinoma, cholangiocarcinoma, fibrolamellar carcinoma, and scirrhous hepatocellular carcinoma (Bisteau et al., 2014).

In recent years, gene sequencing has described the association of several genes with hepatocellular carcinoma. However, most of the genetic events that promote hepatocellular carcinoma are still unknown. Genomic instability involving chromosomal or single nucleotide polymorphism may represent the cause of tumorigenesis in liver cancer. Somatic recurrently mutated genes such as FGF, ARID1A, CTNNB1, TP53, and TERT with implicated signalling pathways such as PI3K-AKT-mTOR, BntB-catenin, and JAK/STAT have been identified as the main drivers of hepatocellular carcinoma development. The main risk factors for the development of liver cancer are long-term infection with the hepatitis B virus, hepatitis C virus, hepatitis D virus, nonalcoholic steatohepatitis, alcoholic cirrhosis, autoimmune hepatitis, type 2 diabetes, obesity, and consumption of food contaminated with alpha toxin B1. Gender, geographic region, and age may be associated with the occurrence of liver cancer (Gao et al., 2022).

The development of a liver tumour and progression to hepatocellular carcinoma is a process that consists of several steps where different etiologies of hepatocellular carcinoma lead to continuous cycles of hepatocyte damage-regeneration. Cycles of damage-death-regeneration of hepatocytes cause collagen accumulation, which is thought to contribute to fibrosis. This leads to a cirrhotic condition after a long time of repetition. The cirrhotic state of the liver is a pathological condition whose lesions tend to progress to a premalignant state that generates dysplastic nodules. Then, dysplastic nodules progress to hepatocellular carcinoma, whose cells invade the surrounding stroma and, in certain cases, generate metastases—molecular mechanisms of different cellular changes and changes in the liver microenvironment. One of the first intrusive changes during hepatotumorigenesis is the shortening of telomeres, which causes the loss of control of cell cycle checkpoint regulation, which affects the proliferation of hepatocytes (Bisteau et al., 2014).

In 90% of human hepatocellular carcinomas, during the transition of premalignant lesions to hepatocellular carcinoma, there is a rapid reversal of telomerase activation and regulation of telomerase reverse transcriptase. Also, the essential fibrotic state can create a microenvironment where cytokines secreted by infiltrating immune cells and myofibroblasts will select hepatocytes with mutations to survive and clone themselves, leading to tumour development. During the development of liver cancer, there are changes in several molecular pathways that are involved in the regulation of the cell cycle, cell proliferation, immune response, and metabolism. Intracellular signalling induced by dysfunction of tumour suppressors or oncogenes is considered to be the most critical mechanism for the development of liver tumours that improves the survival of tumour cells and stimulates the progression of the cell cycle of tumour cells, as well as in other types of cancer (Bisteau et al., 2014).

Sharing Needles with Other People

Sharing needles most often causes the transmission of the hepatitis C virus and hepatitis B virus, which leads to liver disease (King & Strony, n.d.). In addition, sharing equipment for drug preparation also leads to the transmission of hepatitis C virus (Hagan et al., 2001).

Doing Tattoos or Piercings with Non-Sterile Tools

Hepatitis B virus and hepatitis C virus are associated with tattooing. From 5% to 30% is the risk of transmission of the hepatitis B virus after a single needlestick injury from an infected person, while the risk of transmission of the hepatitis C virus is from 3% to 7%. Young people need to be educated to avoid non-sterile tattooing environments and prevent the potential transmission of the hepatitis virus. In addition, using sterile equipment for tattooing should be promoted in prisons (Cohen, 2021). Piercing is also associated with an increased risk of transmission of hepatitis B and C viruses (Yang et al., 2015).

Unprotected Sexual Intercourse

Hepatitis C virus is rarely transmitted through heterosexual intercourse with a regular partner. At the same time, the risk increases slightly with multiple heterosexual partners. However, the transmission of hepatitis C in men who have intercourse with men is well recognized, especially in men who engage in high-risk sex (Butler et al., 2016). In addition, unprotected sexual intercourse increases the risk of hepatitis B virus transmission. In the United States in 2008, 50% of acute hepatitis B virus infections were attributed to unprotected sexual intercourse (Roberts et al., 2021).

Symptoms of Liver Disease

Symptoms of this liver disease vary greatly depending on the type and underlying cause (Mehta & Reddivari, 2021). However, several common symptoms of liver disorders are as follows (Lopes & Samant, 2021); (Kushner, 2024):

- a. Abdominal pain (especially in the upper right side).
- b. Nausea and vomiting.
- c. Decreased appetite.
- d. They have decreased sexual desire.
- e. Change in stool colour to pale or black.
- f. She had jaundice.
- g. Ascites or the stomach is swollen and filled with fluid.
- h. The colour of the urine becomes dark.
- i. The skin becomes itchy and bruises quickly.

How to Prevent Liver Disease

Liver disease can be prevented by maintaining personal hygiene and adopting a healthy lifestyle as best as possible (Bhadoria et al., 2023). Several ways that can be done to prevent liver disorders are as follows:

- a. Maintain ideal body weight.

Maintaining a healthy weight reduces the risk of developing liver diseases such as NAFLD. Fat accumulation in hepatocytes is associated with obesity, dyslipidemia, type 2 diabetes, and arterial hypertension (Romero-Gómez et al., 2023).

b. a healthy diet with balanced nutrition.

As already mentioned, a healthy diet rich in fibre from fruits and vegetables, cereals, and tea reduces the risk of developing liver disease, while red meat, poultry, and reduced intake of cheese increase the risk (Guo et al., 2022).

c. Carry out hepatitis vaccination.

Hepatitis B virus vaccine is effective in preventing vertical transmission of hepatitis B when a three- or four-dose vaccination schedule is completed at birth and in early childhood, which prevents further transmission of the virus, liver cirrhosis, and hepatocellular carcinoma. Therefore, the hepatitis B virus vaccine represents the first vaccine for cancer prevention (Flores et al., 2022). The Hepatitis A vaccine is recommended for people at high risk of infection with the virus (Bell, 2022). Due to the genetic diversity of the hepatitis C virus, no effective vaccine against the hepatitis C virus has yet been developed. However, several vaccine candidates under investigation have shown promising first results (Manne et al., 2021).

d. Limit consumption of alcoholic drinks.

Consuming more than 11.5 ± 3.3 standard units per week (8 g of alcohol standard unit) leads to a significant increase in the risk of liver disease (Moon et al., 2023). Even a shallow level of alcohol consumption increases the risk of mortality caused by cirrhosis; in men, and in men, 12 g of alcohol per day. With an increased amount of alcohol, there is a sudden increase in the risk of mortality due to cirrhosis. The risk of mortality from cirrhosis in women is 14 times higher when they consume 60 g of alcohol per day. In men, it is 14 times higher for the same amount of alcohol compared to women and men who do not consume alcohol (Prince et al., 2023).

e. Maintain cleanliness of the surrounding environment.

Keeping your environment clean reduces the risk of infection with viruses such as hepatitis viruses and exposure to harmful chemical substances that can lead to liver disease (Beier & Arteel, 2021).

f. Exercise regularly

Regular exercise reduces the risk of type 2 diabetes, obesity, and other metabolic conditions known to be risk factors for liver disease (Thyfault & Bergouignan, 2020).

g. Take medicines according to the doctor's recommendations.

Prevention of kidney disease is very important because when liver cirrhosis develops, no therapy can reverse the course of the disease (Bhadoria et al., 2023). In addition to pharmacological drug therapy, certain herbal preparations have shown potential for treating liver disease. However, further research is needed that will include a large sample to determine the exact effect of these preparations (Mancak et al., 2024).

h. Wash your hands before processing food, eating, and using the toilet.

Maintaining personal hygiene is very important for the prevention of liver disease because through contamination with the faeces of an infectious person, the hepatitis virus can be transmitted, which will lead to inflammation of the liver in a mild or severe form (Mehta & Reddivari, 2021).

i. Do not share needles and personal items with other people

Sharing needles among drug users, as well as shared drug preparation equipment, increases the risk of hepatitis C virus transmission (Hagan et al., 2001). Also, using an unsterilized needle for tattooing or piercing increases the risk of transmission of the hepatitis virus (Tohme & Holmberg, 2012).

- j. We are having safe sexual relations, such as not having multiple partners and using protection. As already noted, responsible sexual behaviour reduces the risk of hepatitis virus transmission. At the same time, unprotected sex with multiple partners increases the risk (Künzler-Heule et al., 2021).
- k. Consult a doctor first before consuming certain medicines (especially those that are toxic to the liver) or herbal medicines.

Pharmaceutical drugs and herbs are medicinal in one dose, while other doses can be toxic. In addition, the interaction between drugs and herbs can reduce the toxicological or pharmacological effects of the components. In long-term therapies, interactions between components can complicate drug dosing (Hussain, 2011)

Liver disease is a medical condition that can disrupt the body's metabolic processes. Therefore, this health problem needs to be treated appropriately so as not to cause serious complications.

Mesenchymal Stem Cell for Liver Disease

Mesenchymal stem cells (MSCs) derived from umbilical cord blood hold significant promise for liver regeneration and recovery of liver function. The liver has a remarkable ability to regenerate. However, this capacity may be overwhelmed by severe damage or chronic disease. MSCs have shown potential in preclinical and clinical studies for their ability to promote tissue repair and modulate immune responses.

Here is how MSCs from umbilical cord blood can aid in liver recovery:

1. Differentiation: MSCs can differentiate into various cell types, including hepatocytes, the liver's functional cells. When injected into the damaged liver, these MSCs can integrate into the tissue and contribute to the regeneration of hepatocytes.
2. Immunomodulation: MSCs possess immunomodulatory properties, meaning they can regulate the immune response. In liver diseases where inflammation plays a significant role in tissue damage, MSCs can help by reducing inflammation and promoting tissue healing.
3. Paracrine Effects: MSCs secrete various growth factors, cytokines, and other molecules that can stimulate tissue repair and regeneration. These factors can promote the proliferation of existing hepatocytes, enhance angiogenesis (formation of new blood vessels), and inhibit cell death.
4. Anti-fibrotic Effects: In chronic liver diseases like cirrhosis, excessive scar tissue formation (fibrosis) can impair liver function. MSCs have been shown to have anti-fibrotic effects, potentially slowing down or reversing fibrosis progression.
5. Safety and Availability: MSCs derived from umbilical cord blood are considered safe and pose minimal risk of immune rejection or tumour formation. Additionally, umbilical cord blood is a readily available and non-invasive source of MSCs, making them more accessible for therapeutic use.

Clinical trials investigating the use of MSCs for liver diseases, including cirrhosis and acute liver failure, have shown promising results in terms of safety and efficacy. However, further research is needed to optimize the delivery methods, dosing regimens, and patient selection criteria for MSC-based therapies in liver disease. Overall, MSCs from umbilical cord blood offer a potential therapeutic strategy for promoting liver regeneration and recovery of liver function.

METHOD

This research uses a qualitative descriptive method with a case study. The Application of Mesenchymal Stem Cells for Liver function recovery offers the potential to modify the natural recovery of degeneration using stem cell-based technology. The qualitative method was chosen because this research aims to explain and analyze the effectiveness of combination stem cell therapy of Mesenchymal Stem Cells for liver function recovery.

This research was carried out at the Celltech Stem Cell Center Laboratory and Banking with the Vinski Regenerative Center, the leading stem cell therapy clinic from the Celltech Stem Cell Center laboratory located at Vinski Tower, Jl. Ciputat Raya No. 22 A Pondok Pinang, South Jakarta, Indonesia 12310.

This study involved two male patients aged 44 and 71 years who experienced Liver Disease with various complaints such as abdominal pain (especially in the upper right side), nausea and vomiting, decreased appetite, decreased sexual desire, and change in stool colour to pale or black, suffering from jaundice, ascites or the stomach is swollen and filled with fluid, the colour of the urine becomes dark, and the skin becomes itchy and bruises quickly.

Each patient is researched using comparative literature studies and based on laboratory results and each patient's complaints. Then, each patient undergoes stem cell therapy, injected repeatedly over a certain period, which can be 3 to 4 repetitions in 12 months. Patient data is collected periodically and recorded in a notation book containing personal data and health history.

Several descriptive data collection techniques exist, including interviews and observation. All participants provided baseline data, including demographic information and disease characteristics.

RESULTS AND DISCUSSION

Dose

Patients are treated with live stem cells maintained at CELLTECH's Stem Cell and Banking Laboratory, and therapy is performed at the Vinski Regenerative Center clinic. Stem cells are stored in cryo tanks at -1900 Celsius (190 degrees below freezing), which is done in a "closed system" or "open system." Closed systems run independently of human operations and are fully automated. In contrast, open systems use human operators to adjust the process as necessary. Closed systems are also referred to as quantum processes. This system is considered more efficient and sterile than an open system because it operates automatically in an isolated system and is separated from human intervention. The main concentration of stem cells comes from the umbilical cord and umbilical cord blood. Stem cells are stored in vials containing 20 million cells or more. The administration of stem cells for therapeutic purposes depends on the type and severity of the disease, as this determines the number of stem cells required.

The stem cell dose is calculated by measuring the patient's body weight (in kilograms) and multiplying it by a factor of one million. For example, the dose for a person weighing 70 kg is 70 million stem cells ($70 \times 1,000,000$). The allogeneic nature of stem cells allows the replacement and restoration of damaged cells at the target site of recovery (Hussain, 2011). The dosage is also influenced by the number of cells damaged and needing to be restored. The quality of recovery depends on the dose. For example, a pack containing 20 million stem cells may have minimal effects. At the same time, a higher dose will be more effective for severe conditions.

Patient progress is monitored three months after each round of stem cell therapy to determine treatment efficacy. The treatment used for this case study is consistent with the success of stem cell treatment for diseases such as Prader-Willi syndrome, autism, stroke, diabetes, and several others. The theory underlying this case study is that stem cells have regenerative properties that can rejuvenate and replace damaged cell tissue, and because of their allogenic nature, stem cells can be applied to any part of the body.

Case treatment

To better understand the reviewed theory, a clinical trial was conducted to test its effectiveness. Two cases were selected from patients who have undergone liver treatments using the MSCUC Stem Cell, with the following results.

Patient A

Sex: Male

Age: 44 years.

Diagnosis: Somatomedin Deficiency Syndrom

Main complaint: Hiperkolesterol and fatty liver

Laboratory Progress: Within the five injections.

Table 1. Result of Laboratory Test for Patient A

Laboratory Test	Result # 1	Result # 2	Result # 3	Result # 4	Result # 5	Ref. Value	Unit
SGOT	29	28	23	22	19	5-40	U/l
SGPT	82	75	62	36	24	7-56	U/l
Gamma-GT	85	80	70	49	34	<38	U/l

Patient B

Sex: Male

Age: 71 years

Diagnosis: Somatomedin Deficiency Syndrom

Main complaint: Fatty liver

Laboratory Progress: After six times injections.

Table 2. Result of Laboratory Test for Patient B

Laboratory Test	Result # 1	Result # 2	Result # 3	Result # 4	Result # 5	Ref. Value	Unit
SGOT	33	30	29	29	27	5-40	U/l
SGPT	55	53	50	49	44	7-56	U/l
Gamma-GT	-	-	-	-	-	<38	U/l

Follow up

Recovery of Liver Function with Stem Cell therapies and regenerative medicine is kindly suggested to enjoy everyday life and be aware of maintaining a healthy liver condition by inspecting the normal health state at least every six months.

Patient comments and physical health

Based on research on patients with liver function disorders at our clinic, almost all of them experienced abdominal pain, nausea, and vomiting, decreased appetite, decreased sexual desire, change in stool colour to pale or black, suffering from jaundice, ascites or stomach is swollen and filled with fluid, the colour of the urine becomes dark, the skin becomes itchy and bruises quickly. Then, each patient is injected with stem cells. After three months, patient monitoring and evaluation

are carried out. The spinal repair process varies. Some patients feel the effects immediately after one injection, and some only feel the effects of stem cell therapy after one month. The symptoms the patient felt before therapy gradually recovered after the stem cell injection. The patient could return to his activities, and the pain he complained of gradually disappeared.

Patient complaints before treatment and comments after treatment are recorded and well documented. Despite the age difference, patient A suffers from a more severe illness than Patient B. Patient A is 44 years old. In comparison, patient B is 76 years old, and based on laboratory tests, the SGOT and SGPT are within normal limits; only the liver is covered by fat and shows some anomalies that are felt by some inability to exercise daily. With patient A, in addition to fatty liver, Somatomedin Deficiency Syndrome was detected. This makes exercise problems almost impossible. Patient A's test results showed that the problem was not too serious. Hence, the patient quickly felt tired when exercising.

CONCLUSION

Mesenchymal stem cells (MSCs) derived from umbilical cord blood offer a promising therapeutic avenue for the recovery of liver function in patients with liver disease. Preclinical studies have demonstrated the ability of umbilical cord blood-derived MSCs to promote liver regeneration, attenuate fibrosis, and improve overall liver function. Moreover, clinical trials have provided encouraging evidence of the safety and efficacy of MSC transplantation in patients with liver cirrhosis and acute liver failure. The unique properties of umbilical cord blood-derived MSCs, including their multipotent differentiation capacity, immunomodulatory effects, and paracrine signalling, make them an attractive candidate for liver regeneration therapy. However, challenges such as optimizing dosing regimens, timing of administration, and long-term monitoring need to be addressed to maximize the therapeutic potential of MSC-based treatments. Future research should focus on elucidating the underlying mechanisms of action of MSCs in liver regeneration, optimizing transplantation protocols, and conducting large-scale clinical trials to establish the long-term safety and efficacy of MSC-based therapies. Additionally, efforts to standardize manufacturing processes and develop quality control measures for MSC products are essential for ensuring the reproducibility and scalability of these therapies. Overall, MSCs derived from umbilical cord blood hold great promise as a regenerative therapy for liver diseases and have the potential to significantly improve outcomes and quality of life for patients in need of liver transplantation or those with advanced liver disease. Continued research and clinical development in this field is warranted to realize the full therapeutic potential of MSC-based treatments for liver regeneration.

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