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*Review Article*

# The Clinical Use of Stem Cells in Liver Cancer Treatment: Interactions Between Diet, Metabolic Disease and Hepatic Regeneration

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## Abstract

Hepatocellular Carcinoma (HCC) is the most frequent primary liver cancer and a leading cause of cancer-related death globally. HCC typically develops in the presence of chronic liver disease, such as cirrhosis, Non-Alcoholic Fatty Liver Disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Underlying liver damage limits treatment options and contributes to poor clinical outcomes. This review examines the pathophysiological progression from NAFLD and NASH to cirrhosis and ultimately HCC, with emphasis on insulin resistance, chronic inflammation, oxidative stress and fibrosis. These interrelated pathways accelerate disease progression and create conditions conducive to tumor formation while reducing the liver's ability to repair itself. It also explores the therapeutic potential of stem cell-based treatments, including induced pluripotent stem cells (iPSCs), hepatic progenitor cells and mesenchymal stem cells (MSCs). These therapies have been studied for their ability to reduce inflammation, promote tissue regeneration and improve liver function in patients with chronic liver disease and HCC. Although early clinical trials show encouraging outcomes, long-term safety concerns and variability in treatment protocols remain challenges. Recent research highlights how dietary and metabolic factors influence disease progression and treatment effectiveness. Dietary patterns affect key processes, including immune activation and lipid metabolism, thereby impacting both liver injury and regenerative capacity. These findings suggest that nutrition is a modifiable factor influencing disease progression and therapeutic response. Overall, stem cell-based therapies may provide benefits as adjuncts to existing treatments, but their effectiveness is influenced by the metabolic context in which they are used.

**Keywords:** Hepatocellular Carcinoma; Stem Cell Therapy; NAFLD; Liver Regeneration; Metabolic Dysfunction

## Introduction

The liver is a crucial organ responsible for several essential physiological functions, which include metabolism detoxification, nutrient storage and regulation of systemic energy balance. It possesses a remarkable regenerative capacity that allows tissue restoration (under normal physiological conditions) following injury. The liver is particularly sensitive to dietary imbalance and metabolic stress due to its prominent role in metabolic homeostasis. Previous studies have shown that high-fat diets can induce structural and inflammatory changes within hepatic tissue, including lipid accumulation, cellular degeneration and inflammatory cell infiltration; all of which contribute to progressive liver dysfunction [1]. Over time, persistent metabolic injury and chronic inflammation may increase susceptibility to fibrosis, cirrhosis and HCC.

As one of the primary causes of cancer-related death globally, HCC represents a substantial and growing global health burden [2,3]. The fact that HCC rarely develops in isolation is one of its distinctive features. Rather, it usually occurs in the context of chronic liver disease, where long-term damage encourages the development of cancer. This underlying disease process distinguishes HCC from many other malignancies and poses unique challenges for detection and treatment.

Persistent inflammation, fibrosis and recurrent cycles of hepatocyte injury and regeneration are the hallmarks of chronic liver disease. These mechanisms cause the liver to undergo structural and functional changes throughout time, including modifications to cellular signaling pathways, extracellular matrix composition and vascular architecture [4]. These alterations raise the risk of tumor development by causing genomic instability and dysregulated cell proliferation [5]. Clinically, this explains why treatment outcomes are still restricted despite advancements in therapeutic alternatives and why HCC is frequently detected at advanced stages.

The fundamental causes of HCC have changed significantly in recent years. Although viral hepatitis, especially hepatitis B and C, has historically been the main cause, fatty liver disease linked to metabolic dysfunction is also becoming a significant factor, particularly in industrialized nations [6,7]. This alteration reflects more general lifestyle changes, such as eating more calorie-dense, low-nutrient foods and engaging in less physical activity. Consequently, diseases like obesity, insulin resistance and type 2 diabetes have been more closely associated with the development of HCC and the advancement of liver disease.

This evolving understanding has important implications for how HCC is conceptualized; rather than being viewed solely as a malignancy, HCC can be understood as the result of prolonged metabolic and inflammatory stress. This perspective highlights the critical role of the hepatic microenvironment in disease development. Factors such as oxidative stress and lipid accumulation do not act independently but instead interact to promote both liver injury and tumor formation [8]. The progression of chronic liver disease to HCC follows a well-characterized sequence (Fig. 1).

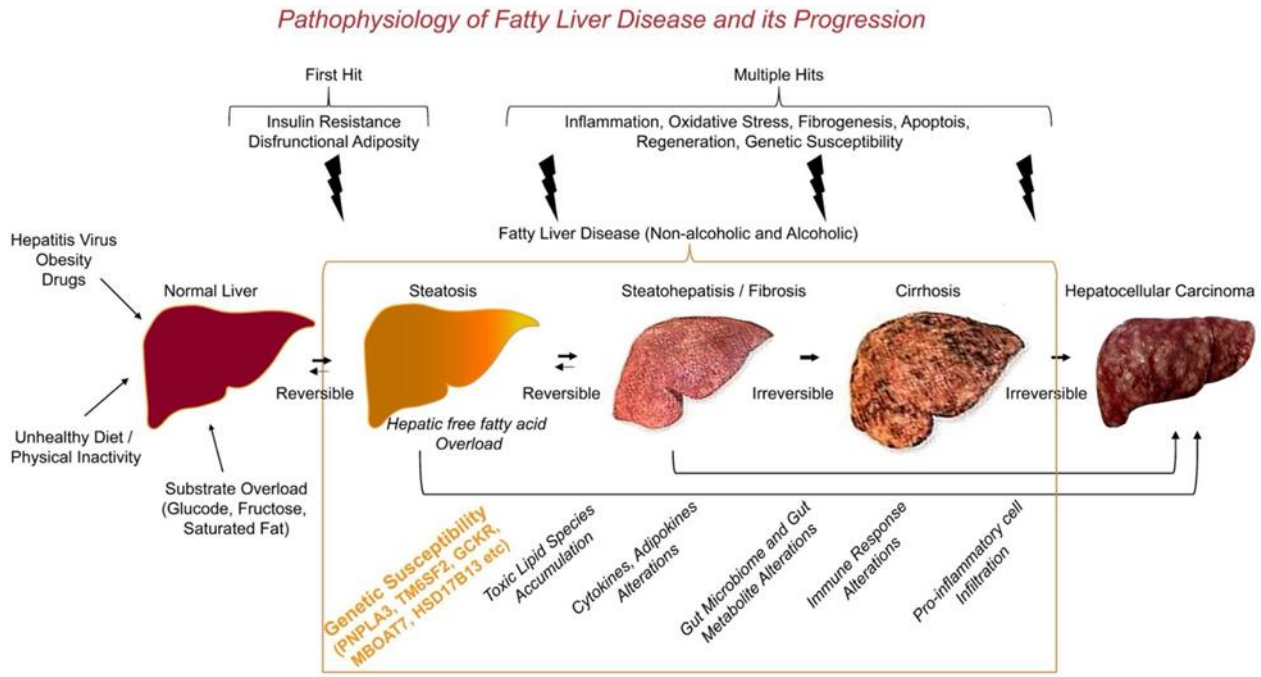


**Figure 1:** Progression of chronic liver disease from NAFLD to HCC, highlighting key intermediate stages, including NASH, fibrosis and cirrhosis [9].

Surgical resection, liver transplantation and systemic therapies are some of the current HCC therapy approaches that have increased patient survival. However, the degree of underlying liver malfunction and the diseased liver's diminished capacity for regeneration frequently restrict their efficacy [10]. Due to this restriction, there is growing interest in alternative strategies that address impaired liver regeneration in addition to focusing on tumor burden.

Among such approaches, stem cell-based treatments are attracting attention because of their capacity to promote tissue repair and alter the hepatic environment. These treatments aim to reduce fibrosis and inflammation while simultaneously enhancing the liver's regenerative capacity. At the same time, it is becoming increasingly clear that dietary and metabolic factors are important in determining how a disease develops and how well a treatment works. Oxidative stress, inflammatory signaling and systemic metabolism are all influenced by diet and are major causes of liver disease [11].

When combined, these findings show that HCC management requires a more comprehensive strategy. Developing more efficient and long-lasting treatment plans requires an understanding of the relationship between tumor biology, liver regeneration and metabolic health. The article will investigate these connections, paying special attention to the role of stem cell-based treatments and the impact of dietary and metabolic factors on the course of liver disease and the outcomes of treatment.

**Pathophysiology of Liver Disease and Cancer**

HCC is a multistep process that develops because of gradual structural damage, metabolic dysfunction and chronic liver injury. HCC usually develops following years of disease progression along the spectrum of cirrhosis, fibrosis, NASH and NAFLD, rather than as a single occurrence [12]. It is essential to comprehend this process because each stage increases the danger of cancer and the liver's diminishing capacity to recover.

Triglyceride accumulation in hepatocytes is a characteristic of NAFLD, which is the first stage. Obesity, insulin resistance and metabolic syndrome are closely linked to this disorder [13,14]. NAFLD produces a metabolic condition that puts the liver at risk for further damage, even though it may remain relatively stable in some people. Hepatocellular damage, inflammation and ballooning degeneration characterize NASH, which develops from NAFLD in about 20–30% of patients [15]. Because NASH is intimately linked to the formation of fibrosis and the long-term course of the illness, this change is clinically significant.

This process is largely influenced by insulin resistance, which modifies hepatic and systemic metabolism. It causes adipose tissue to undergo more lipolysis, which raises the amount of free fatty acids in the blood, which the liver then absorbs [16-18]. The generation of reactive oxygen species, which fuel oxidative stress and cellular damage and mitochondrial dysfunction is caused by these excess lipids. Hepatic steatosis is made worse by insulin resistance, which also encourages de novo lipogenesis in hepatocytes. Oxidative stress and lipid overload combine to produce an injury loop that gets harder to break. These interconnected metabolic and inflammatory pathways contribute to liver disease progression (Fig. 2).

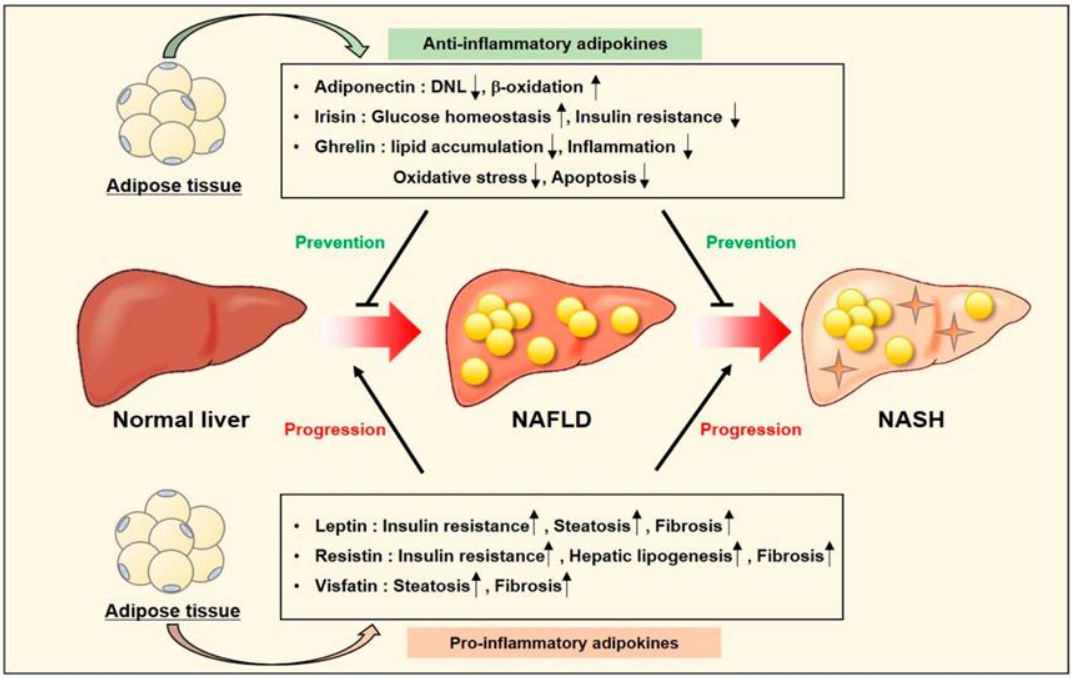


**Figure 2:** Metabolic and inflammatory mechanisms contributing to liver disease progression, including the role of adipokines, insulin resistance and lipid accumulation [19].

Liver damage is amplified by persistent inflammation. When hepatocyte damage occurs, the liver's resident macrophages, known as Kupffer cells, become activated and release pro-inflammatory cytokines like Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-$\alpha$) [20,21]. These cytokines maintain a chronic inflammatory state by recruiting more immune cells in addition to prolonging hepatocellular damage. Hepatic stellate cells, the main mediators of fibrosis, are activated concurrently by inflammatory signals [22]. Extracellular matrix proteins are deposited by activated stellate cells, which progressively replace normal liver tissue with fibrotic scar tissue.

The liver experiences substantial structural alterations as fibrosis advances, which hinder both regeneration and function. The last stage of this process is cirrhosis, which is marked by significant scarring, changed vascular architecture and the development of regenerating nodules [4]. Through repeated cycles of cell death and regeneration, this modified microenvironment increases genomic instability and boosts the risk of mutations in tumor suppressor and oncogene genes [23]. This provides a clinical explanation for why cirrhosis is one of the biggest risk factors for the development of HCC.

Dietary factors are increasingly recognized as active contributors to disease pathogenesis and play a crucial role throughout this process. The advancement of NAFLD is accelerated by diets heavy in refined carbohydrates, especially fructose, which increases insulin resistance and encourages hepatic lipogenesis [24]. In a similar vein, consuming large amounts of saturated fats causes inflammation and cholesterol buildup in the liver. On the other hand, diets high in fiber, antioxidants and unsaturated fats—such as the Mediterranean diet, which emphasizes fruits, vegetables, whole grains, legumes, olive oil, nuts and fish—have been associated with improved metabolic control and reduced inflammatory signaling [25,26].

These results demonstrate that dietary intake has a direct impact on the biological processes that cause liver disease rather than just being linked with it. Dietary patterns can influence the development of liver disease as well as the liver's ability to regenerate by influencing oxidative stress and lipid metabolism. This has important clinical implications, as it identifies diet as a modifiable factor that may complement both conventional and regenerative therapies [25,26].

**Stem Cells in Liver Regeneration and Cancer Therapy**

Stem cell–based therapies have emerged as a promising area of research in the treatment of chronic liver disease and HCC, primarily due to their potential to enhance liver regeneration and modulate the hepatic microenvironment. Unlike conventional therapies that focus primarily on tumor removal or suppression, stem cell approaches aim to address the underlying impairment in liver function that limits treatment success.

Among the various stem cell populations studied, MSCs are the most extensively investigated. MSCs are relatively accessible for clinical usage since they can be extracted from a variety of sources, such as bone marrow, adipose tissues and umbilical cord blood [27-29]. Their ability to release bioactive substances that affect the surrounding cellular environment, such as growth factors, cytokines and extracellular vesicles, is largely responsible for their therapeutic effects.

Paracrine signaling is one of the main methods through which MSCs work. MSCs release molecules that lower inflammation, prevent apoptosis and encourage tissue repair instead of directly developing into hepatocytes [30]. By boosting anti-inflammatory signaling pathways and reducing the generation of pro-inflammatory cytokines, these signaling molecules can regulate immune responses. This is particularly important in chronic liver disease, where persistent inflammation plays a central role in disease progression. MSCs have been demonstrated to affect fibrosis in addition to their immunomodulatory actions by preventing hepatic stellate cell activation and encouraging extracellular matrix remodeling. The liver's architecture may be restored and general function may be enhanced by this antifibrotic impact. Additionally, MSCs can promote angiogenesis and increase the survival of preexisting hepatocytes, which enhances their ability to regenerate. MSCs exert their therapeutic effects through multiple regenerative and immunomodulatory pathways (Fig. 3).

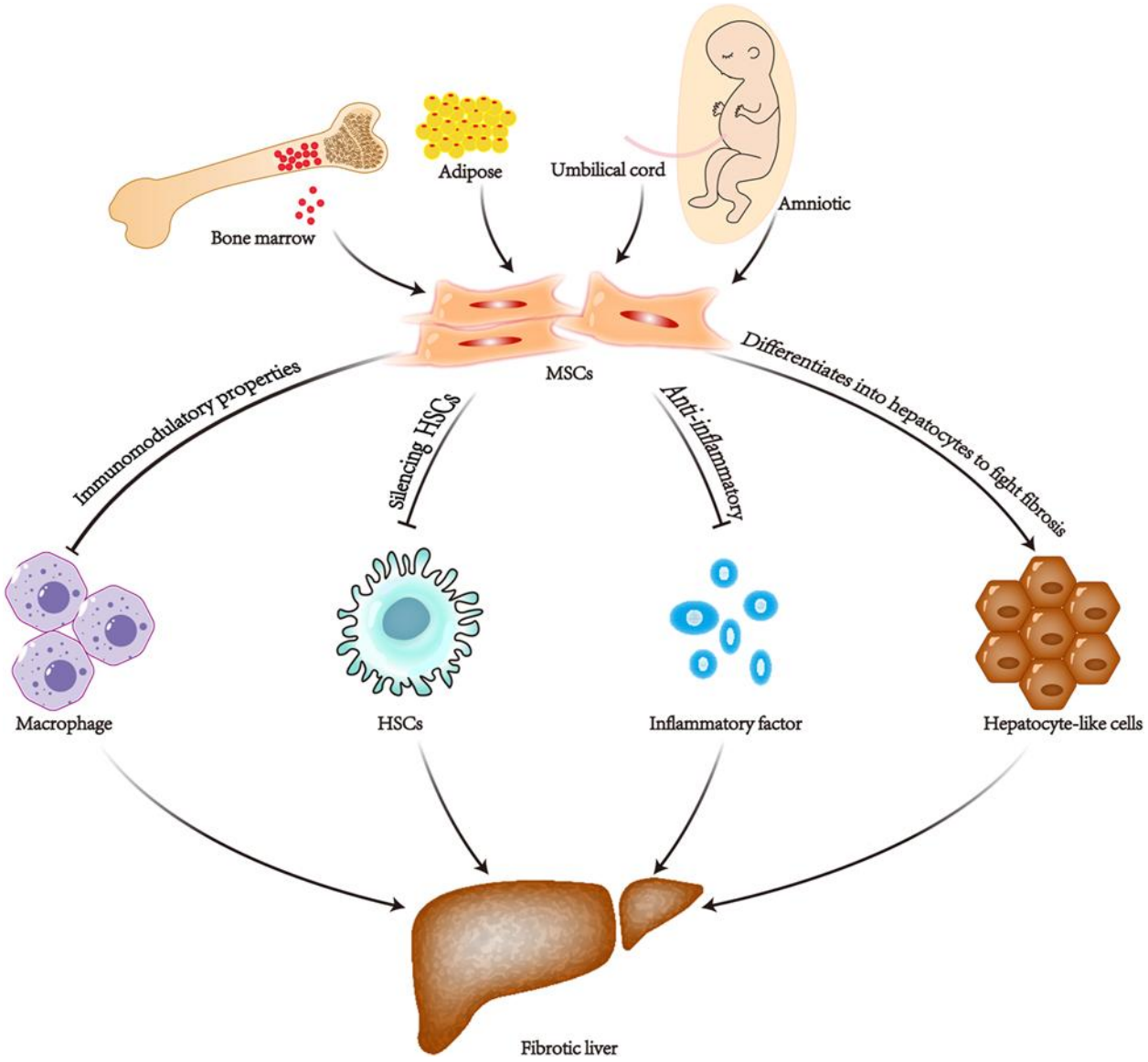


**Figure 3:** Proposed mechanisms of Mesenchymal Stem Cell (MSC) therapy in liver disease, including immunomodulation, anti-inflammatory effects, inhibition of hepatic stellate cells and promotion of tissue regeneration [31].

Hepatic progenitor cells represent another important population involved in liver regeneration. These cells are found in the liver naturally and become active when hepatocyte proliferation is hindered. They are an essential part of the liver's natural healing processes since they can develop into both hepatocytes and biliary cells. However, these cells' ability to regenerate is frequently insufficient to make up for continuous damage in late liver disease.

iPSCs offer additional therapeutic potential due to their ability to generate patient-specific hepatocyte-like cells [32]. One benefit of this strategy is that it lowers the possibility of immune rejection. However, issues with tumor development, insufficient differentiation and genetic instability continue to restrict the clinical use of iPSCs.

Clinical research on stem cell therapies for liver disease has shown encouraging but inconsistent outcomes. Following MSC delivery, improvements in liver function markers, such as serum albumin levels and Model for End-Stage Liver Disease (MELD) scores, have been observed in several early-phase trials [33,34]. Additionally, several studies have shown increases in patient quality of life and decreases in fibrosis. Long-term advantages are yet undetermined, though and these results are inconsistent among research [33]. The lack of standardization among clinical studies is a significant obstacle in the field. It is challenging to evaluate outcomes and reach firm conclusions due to variations in stem cell sources, dosage schedules, delivery techniques and

patient groups. Furthermore, limited information is known about the durability and functional integration of transplanted cells. The therapeutic results are frequently temporary, indicating that additional treatments may be required [32,34].

Concerns about safety are still of considerable significance. Although MSCs are usually thought to have a good safety profile, there is continuous discussion on whether they could, in some circumstances, encourage tumor growth [35,36]. Because the hepatic milieu already encourages abnormal cell proliferation in HCC, this issue is more pertinent. One major obstacle to the clinical use of pluripotent stem cells is the possibility of unchecked differentiation and teratoma development [35].

Stem cell-based therapies still have considerable potential as supplemental therapy for HCC and liver disease despite these obstacles. They are a desirable alternative for resolving the shortcomings of existing treatments because of their capacity to alter the hepatic environment, lower inflammation and promote regeneration. However, the state of the liver environment in which they are introduced is likely to have an impact on their efficacy, in addition to the characteristics of the cells themselves [36].

**Diet, Metabolic Health and Stem Cell Function**

Metabolic health plays a central role in both the progression of liver disease and the effectiveness of emerging regenerative therapies. Conditions such as obesity, insulin resistance and dyslipidemia alter the systemic and hepatic environment in ways that directly impact cellular signaling, immune function and tissue repair [37,38]. In this context, the liver is not functioning in isolation but is instead responding to broader metabolic inputs, many of which are strongly influenced by diet.

Chronic low-grade inflammation is one of the primary mechanisms connecting liver disease and metabolic health. Adipose tissue produces pro-inflammatory cytokines, such as TNF-$\alpha$ and IL-6, which circulate throughout the body and cause hepatic inflammation in metabolically dysregulated situations [39-41]. In addition to causing hepatocellular damage, this ongoing inflammatory signaling disturbs the hepatic stem cell niche, which is a unique cellular environment that controls stem cell survival, development and function [42].

Endogenous regeneration and the effectiveness of stem cell-based treatments are both significantly impacted by disruption of the hepatic stem cell niche. Oxidative stress and inflammatory signaling can change differentiation pathways, decrease the efficacy of regenerative signaling and affect stem cell viability [43]. Therefore, even if stem cells are used therapeutically, the surrounding metabolic conditions may impair their capacity to perform at their best. This highlights the importance of considering systemic factors when evaluating regenerative therapies.

One of the most significant modifiable elements affecting metabolic health and, consequently, the progression of liver disease is diet. Insulin resistance, hepatic lipogenesis and chronic inflammation have all been linked to diets heavy in refined carbs, added sugars and ultra-processed foods [11,44]. Fructose is mostly processed in the liver and has been closely linked to elevated oxidative stress and de novo lipogenesis, both of which accelerate the development of NAFLD. The impact of dietary patterns on liver disease progression is summarized in Table 1.

| Dietary Pattern | Effect on Liver Disease |
|---|---|
| High sugar / refined carbohydrates | Increase insulin resistance, increase hepatic lipogenesis |
| Saturated fats | Increase lipid accumulation, increase inflammation |
| Ultra-processed foods | Increase oxidative stress, increase NAFLD progression |
| Mediterranean diet | Decrease inflammation, increase insulin sensitivity |
| High fiber / antioxidant-rich foods | Decrease oxidative stress, improved metabolic health |

**Table 1:** Impact of dietary patterns on liver disease progression.

On the other hand, dietary patterns that prioritize whole foods, including fruits, vegetables, whole grains, lean proteins and unsaturated fats, have been linked to better metabolic results and lower levels of inflammation [45]. For instance, it has been demonstrated that the Mediterranean diet increases insulin sensitivity and lowers inflammatory markers, which may indirectly enhance liver function and decrease the progression of illness. From a mechanistic standpoint, these eating habits affect several important pathways related to liver disease. Antioxidant-rich foods may reduce oxidative stress and dietary fiber promotes the

integrity of the gut flora, which influences hepatic inflammation and immunological signaling [46]. These consequences demonstrate how food, metabolism and liver function are interrelated.

Most importantly, dietary adjustments can drastically change the course of the disease, even if they are unlikely to reverse advanced liver disease or eradicate cancer on their own. Diet may reduce the severity of liver damage and improve the environment for regeneration by enhancing metabolic health. This could improve the efficacy of both traditional therapy and new regenerative treatments, such as stem cell-based methods [40,43].

These results offer credence to a more comprehensive understanding of liver disease, in which nutrition plays an active role in both the course of the condition and the response to treatment. Understanding this connection may help develop more all-encompassing treatment plans that target the processes limiting healing as well as the underlying causes of liver damage.

**Clinical Implications and Future Directions**

HCC is complicated and multifaceted, which stresses the need for a more comprehensive approach to treatment. Tumor burden is the primary focus of conventional therapy, such as liver transplantation, surgical resection and systemic medications. Nevertheless, these methods frequently fall short in addressing the underlying liver malfunction that hinders recovery and advances the disease [47]. By focusing on the liver's capacity for regeneration, stem cell-based treatments present a potential way around this restriction. However, the state of the hepatic environment in which they are used is likely to impact how effective they are. As was mentioned, metabolic dysfunction, fibrosis and persistent inflammation are all capable of having significant impacts on treatment results. This implies that treatments that enhance metabolic health may work best in conjunction with stem cell therapy.

This approach is consistent with personalized medicine's tenets. The disease stage, liver function, metabolic status and responsiveness to treatment of patients with HCC vary greatly. Therefore, a uniform treatment strategy is unlikely to be effective. Rather, treatment plans might need to be customized to each patient's unique profile, accounting for both environmental and biological aspects. These tailored strategies may be significantly influenced by biomarkers of fibrosis, inflammation and metabolic dysfunction. Patients who are more likely to benefit from combined metabolic and regenerative therapy, for instance, may be identified by measurements of insulin resistance or inflammatory markers. This strategy could benefit patient selection and maximize therapeutic results [32,43].

Despite the potential benefits of stem cell treatments, there are still several unanswered questions. Small sample numbers, brief follow-up times and inconsistent methods are common limitations of research [48]. It is challenging to evaluate long-term safety and effectiveness because of these restrictions. Furthermore, limited information is available about the long-term interactions between transplanted stem cells and the damaged hepatic environment. Large-scale, well-controlled clinical trials that assess both immediate and long-term results should be the main focus of future studies. Improving repeatability and comparability between trials will require standardization of stem cell sources, dosage plans and delivery techniques [32,46].

Understanding how metabolic health and regenerative medicines interact is of equal importance. Research on the effects of dietary treatments on liver regeneration and stem cell function may yield important information for improving treatment approaches. Given the rising incidence of metabolic liver disease, this field of study is very relevant. Ultimately, treating HCC may require a multimodal strategy that incorporates metabolic control, regenerative medicine and cancer-directed therapies [32,43,45]. This strategy offers the potential to increase patient survival and quality of life by treating the tumor as well as the environment in which it grows.

**Conclusion**

HCC is a complex disease that arises when metabolic dysfunction and persistent liver damage are present. Insulin resistance, chronic inflammation, oxidative stress and fibrosis are among the interrelated pathways that propel the development of NAFLD, cirrhosis and eventually HCC. These mechanisms aid in the growth of tumors and hinder the liver's capacity to repair, making treatment extremely difficult. By promoting tissue regeneration and altering the hepatic environment, stem cell-based treatments present a viable way to overcome these restrictions. However, the metabolic conditions under which they are used have a significant impact on their efficacy. It becomes clear that diet and metabolic health are significant, modifiable factors of this

process. Dietary habits can affect how the disease progresses and how well a patient responds to treatment by altering important pathways involved in liver injury and regeneration. Dietary interventions may significantly improve clinical outcomes, even though they are not curative. When combined, these results emphasize the significance of a comprehensive approach for managing HCC that incorporates metabolic treatments, regenerative medicine and tumor-directed therapy. Continued research will be essential to better understand these relationships and to develop strategies that improve both the effectiveness and sustainability of treatment.

**Conflict of Interest**

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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**Data Availability Statement**

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

**Ethical Statement**

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

**Informed Consent Statement**

Informed consent was obtained from all participants included in the study.

**Authors' Contributions**

All authors contributed equally to this paper.

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