

Review

# The IGF/IGFR System During Chronic Liver Disease: Role in Neurocognitive Complications and Aging

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[Received May 11, 2026; Revised July 28, 2026; Accepted July 30, 2026]

**ABSTRACT:** Aging is associated with a significant functional impairment of different organs, including liver, and it increases sensitivity to the development of liver-related complications. In fact, advanced chronic liver disease is higher in aged populations and is associated with worse prognosis. These patients frequently show a dysfunctional liver-brain axis and exhibit mild neurocognitive dysfunction, which significantly impairs quality of life. The insulin-like growth factor system is the major endocrine system regulating energy and substrate metabolism, participating also in growth, proliferation and regulation of tissue-specific cell differentiation. Several studies have shown that the IGF1-IGF1R system is significantly altered in CLD contributing to CD4+ T cell activation and differentiation toward Th17, a main driver of the inflammatory microenvironment and liver tissue damage present in these patients. Recent studies highlight the involvement of Th17 cells in cognitive impairment. These cells can breach the blood-brain barrier and exacerbate brain injury in various neurological disorders. Neuroinflammation is also linked to the insulin-like growth factor system, as IGF is involved in the protein synthesis necessary for the growth and survival of different cell populations of the brain, such as neurons, astrocytes and microglia. Thus, an altered IGF/IGFR system is involved in cognitive decline and memory, and several studies have revealed its implication in aging and cell senescence. This narrative review summarizes the participation of the IGF/IGFR system in chronic liver disease, focusing on its multifactorial role on the liver-brain axis and its contribution to inflammatory and neurocognitive complications developed during aging in these patients.

**Keywords:** Chronic liver disease, Aging, IGF1, Brain-liver axis

## Introduction

The insulin-like growth factor system (IGF system) includes two ligands, IGF1 and IGF2, six ligand-binding proteins (IGFBPs), and two receptors, IGF receptor 1 (IGF1R) and 2 (IGF2R) [1]. Both are cell membrane receptors; IGF1R has an intracellular tyrosine kinase domain, which initiates an intracellular signaling cascade upon ligand binding, and both can act as transcription factors after internalization to the cell nucleus; an action that could be regulated by ligand levels. The liver is the

main organ responsible for IGF1 and IGF2 ligand secretion, although other organs and tissues can also secrete some amounts of both ligands, such as the brain, muscles, and kidneys [2]. Once secreted, the ligands bind to their corresponding receptors with high affinity, although they can also bind to insulin receptors [3].

This system stimulates growth, proliferation, and regulates tissue-specific cell differentiation. Along with the growth hormone (GH), the IGF system is the major endocrine system regulating energy and substrate metabolism. IGF1 ligand improves glucose sensitivity

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and uptake, modulates gene and protein synthesis as a transcription factor, and reduces insulin resistance [4]. The IGFBPs function as the critical gatekeepers of the IGF system, modulating bioavailability, transport, and half-life of both IGF1 and IGF2 [1]. Under physiological conditions, IGFBPs can either sequester circulating IGFs to prevent premature receptor activation or, conversely, facilitate their localized delivery and presentation to the IGF1R, modulating survival and metabolic pathways [5]. However, in conditions characterized by severe organ remodeling and metabolic stress, such as advanced hepatic fibrosis and cirrhosis, the systemic and local expression profiles of specific binding proteins shift dramatically, turning these proteins into active drivers of disease progression rather than mere passive transporters [6, 7]. Within this family, IGFBP-3 and IGFBP-7 emerge as pivotal mediators of tissue remodeling and senescence. IGFBP-3 represents the primary systemic carrier of circulating IGF1, synthesized predominantly by hepatocytes, hepatic sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs).

Cirrhosis develops following prolonged inflammation of the liver, in which normal tissue is replaced by fibrotic tissue lacking liver characteristic functions and morphology [8]. The pathology ranges from an asymptomatic phase of compensated cirrhosis to a symptomatic phase where cirrhosis is decompensated, worsening the patients' clinical situation. At this stage, patients often require hospitalization, presenting increased rates of mortality [8, 9]. Patients with advanced chronic liver disease (ACLD) often suffer systemic complications, insulin resistance, and systemic inflammation, which influence disease progression. Clinical complications, such as chronic kidney disease, and hepatic encephalopathy (HE) are common in decompensated cirrhosis. In the case of HE, mild forms are very common in patients with ACLD, compromising patients' quality of life and increasing the risk of overt HE [10]. The liver-brain axis is shaped by highly prevalent metabolic comorbidities, including obesity, type 2 diabetes mellitus (T2DM), sarcopenia, and metabolic dysfunction-associated steatotic liver disease (MASLD). In MASLD and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), chronic hepatic inflammation and progressive fibrosis severely disrupt the physiological production of liver-derived IGF1. This hepatic growth factor deficit directly impairs systemic IGF1 availability [11, 12]. When coupled with the systemic insulin resistance characteristic of obesity and T2DM, the signaling cascade is further compromised. Hyperinsulinemia, in turn, downregulates the hepatic synthesis of IGFBPs, particularly IGFBP-1 and IGFBP-2, altering the circulating ratio of free-to-bound IGF1 and disrupting tissue-specific responsiveness [13, 14].

At the blood-brain barrier (BBB), obesity-induced low-grade systemic inflammation synergizes with diminished IGF1 signaling to compromise endothelial tight junction integrity [15, 16]. This disrupted barrier permits the influx of neurotoxic mediators into the central nervous system (CNS) [17]. Furthermore, metabolic syndrome accelerates cognitive decline through the compounding effect of sarcopenia. The loss of skeletal muscle mass and function severely limits the muscle-derived secretion of neuroprotective factors like irisin and IGF1, worsening the systemic growth factor deficit [18, 19]. Within the CNS, this multi-system metabolic dysfunction impairs mitochondrial energetics, exacerbates neuronal oxidative stress, and drives microglia and astrocytes toward chronic proinflammatory phenotypes [19]. Consequently, the coexistence of these metabolic comorbidities alters the translation of peripheral hepatic dysfunction into accelerated neurodegenerative outcomes.

Several studies have revealed that IGF1 is also involved in aging and cell senescence, which could be related to the differential effect of this ligand in the presence or absence of inflammation [20]. Aging is associated with a significant functional impairment of different organs, including liver, and increases sensitivity to the development of liver-related complications [21, 22]. Systemic metabolic dysfunction observed in patients with MASLD is common in older adults and potentially contributes to cognitive decline and brain structural abnormalities [23].

The incidence of ACLD is higher in aged populations and is associated with worse prognosis [21, 24]. The presence of low-grade inflammation and hepatic vascular resistance induce hepatocyte dysfunction and recruitment of proinflammatory cells supporting the correlation between aging and liver inflammation and dysfunction [25]. In this line, cirrhotic elderly patients show higher in-hospital mortality than non-cirrhotic patients after a routine surgical procedure, pointing out the impact of liver dysfunction on patients' recovery [26]. In addition, patients with cirrhosis showed higher risk of falls but also neuropsychiatric alterations in cognitive, executive and visuospatial functions, correlated with brain white matter alterations [27, 28].

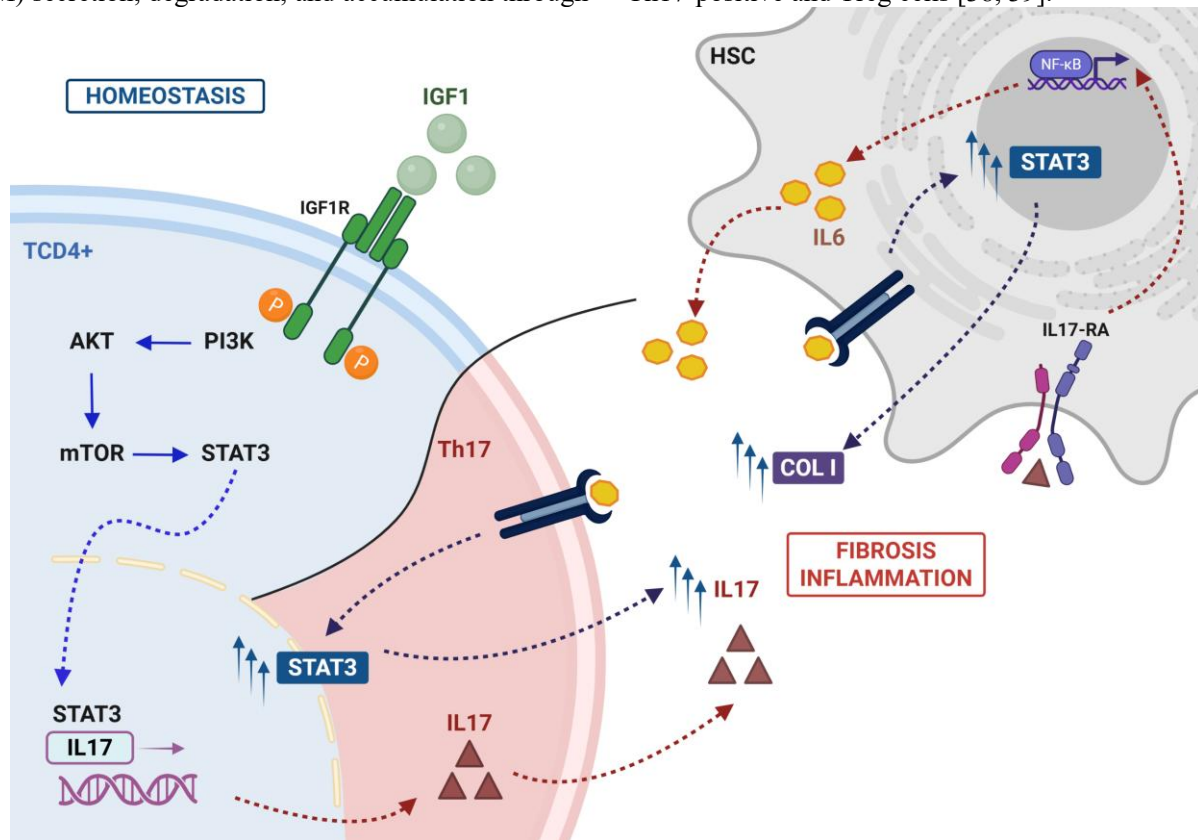
This narrative review summarizes the main findings regarding the participation of the IGF/IGFR system within the proinflammatory environment of CLD, specially focusing on the liver-brain axis and the associated neurocognitive complications developed during aging in these patients.

### **Alteration of the IGF/IGFR system during chronic liver disease**

Chronic liver damage results from untreated liver injury, starting with liver fibrosis induced by a pro-inflammatory state in several parenchymal and non-parenchymal hepatic cell types that ultimately results in cirrhosis, and liver failure [29]. The immune system plays a pivotal role in the pathophysiology of CLD. Among liver functions, the active immune surveillance of signals derived from the gut microbiota constitutes a relevant activity [30, 31]. Under homeostatic conditions, there is a balance skewed towards tolerance between immune cells with a proinflammatory profile, such as adaptive T helper (Th)17, and those with a regulatory role, such as regulatory T cells (Treg). This balance is necessary to maintain the liver role against gut microbiota-related dysbiosis and bacterial translocation [32, 33]

In liver cirrhosis, the Th17 lymphocyte population increases significantly, contributing to the inflammatory microenvironment and chronic damage [34]. In addition, immune cells are strongly involved in extracellular matrix (ECM) secretion, degradation, and accumulation through

their crosstalk with hepatic stellate cells (HSC). Inflammatory cytokines released during fibrosis injure hepatocytes, resulting in the release of reactive oxygen species (ROS) and other cellular contents, directly activating HSCs and contributing to damage chronicity [35]. If damage persists, HSCs and fibroblasts remain continuously activated, releasing ECM and deteriorating liver architecture and function, through the activation of STAT3 involved in HSC survival [36][37]. The interaction between activated HSCs and T lymphocytes regulates the chronic inflammatory microenvironment and promotes damage progression through an imbalance between Th17/Treg cells, where the increase in the Th17 population contributes to the proinflammatory state [34, 38, 39] (Fig. 1). The activation and function of these HSCs are in turn regulated through several cytokines, such as IL-17, IL-10, and TGF- $\beta$ 1, released by proinflammatory Th17 cells [40]. Clinical studies have revealed that HSC activation increased the number of Th17-positive and Treg cells [38, 39].



**Figure 1. Under homeostatic conditions, immune cell populations are balanced.** However, during chronic liver injury, IGF1 binds to its receptor (IGF1R) on CD4<sup>+</sup> T cells, inducing the activation of the PI3K/AKT/mTOR signaling pathway. This cascade promotes the translocation of STAT3 to the nucleus, driving the differentiation of T cells into the Th17 phenotype and increasing IL-17 secretion. Interestingly, IL-17 released by Th17 cells binds to the IL17-RA receptor on HSCs, activating downstream signaling pathways such as STAT3 and NF- $\kappa$ B. This activation induces profound fibrogenic and pro-inflammatory responses in HSCs, significantly upregulating collagen I (COL I) expression and IL-6 secretion. In addition, IL-6 released by HSCs acts back on Th17 cells, establishing a positive feedback loop that further increases STAT3 activation and IL-17 production, consequently exacerbating liver fibrosis and systemic inflammation.

**Table 1.** Overview of relevant studies characterizing the IGF1-IGF1R system alterations in liver disease, organized chronologically.

| Reference                                      | Study Model or Population                                                                               | Biological sample              | Key findings                                                                                                                                                                                                              | Main outcomes                                                                                                                                                                 |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chen <i>et al</i> , 2024 <sup>1</sup>          | NASH patients (N=15) and mouse models (HDL and MCD)                                                     | Liver tissue (RNAseq)          | ↓ IGF1 expression in NASH patients<br><br>Overexpression of MIR22HG promotes autophagy and inhibits pyroptosis and fibrosis through IGF1 pathway.                                                                         | Suggests the IGF1 pathway as a therapeutic target to modulate inflammation and cell death in NASH.                                                                            |
| Wang <i>et al</i> , 2023 <sup>2</sup>          | Mouse model (MCD) and <i>in vitro</i> co-culture                                                        | Hepatocytes and HSC            | Ninjurine2 interacts with IGF1R, increasing hepatocyte secretion of fibrogenic cytokines through IGF1R-PI3K-AKT-EGR1 pathway.                                                                                             | Identifies hepatocyte IGF1R activation as a specific driver of fibrosis progression via paracrine signaling to HSCs.                                                          |
| Mosca <i>et al</i> , 2023 <sup>3</sup>         | Adolescents with obesity and MAFLD (N=191)                                                              | Liver biopsy                   | ↓ IGF1 levels negatively correlated with the degree of fibrosis.                                                                                                                                                          | Highlights the potential of the pharmacological modulation of GH-IGF1 axis in pediatric MASLD.                                                                                |
| Osganian <i>et al</i> , 2022 <sup>4</sup>      | NAFLD cohort (N=318)                                                                                    | Liver tissue                   | ↓ <i>Igf1</i> gene expression with increased NAFLD severity                                                                                                                                                               | Reinforces IGF1-IGF1R pathway as a candidate for therapeutic intervention.                                                                                                    |
| Stanley <i>et al</i> , 2021 <sup>5</sup>       | NAFLD subjects (N=61)                                                                                   | Liver biopsy                   | ↓ <i>Igf1</i> mRNA in high activity NAFLD. Positive association of <i>Igfbp-6</i> and <i>Igfbp-7</i> mRNA levels with NAFLD activity.                                                                                     | Positions the IGF system (including binding proteins) as a potential biomarker of disease stage and severity.                                                                 |
| Alisi <i>et al</i> , 2018 <sup>6</sup>         | Children and adolescents with obesity and NAFLD (N=45)                                                  | Liver biopsy                   | ↑ IGF1R protein expression and ↑ <i>Igf1</i> gene expression in hepatic steatosis                                                                                                                                         | Suggests that IGF1-IGF1R axis alterations track with disease severity in early-onset metabolic liver disease.                                                                 |
| Liu <i>et al</i> , 2016 <sup>7</sup>           | Liver cirrhosis patients and mouse model (CCl <sub>4</sub> )                                            | Serum and liver tissue         | ↓ IGF1 serum levels contrasted with ↑ IGF1R levels in the liver during cirrhosis development.                                                                                                                             | Confirms the inverse correlation between circulating ligand (IGF1) levels and fibrosis while showing receptor upregulation as a local compensatory or pathological mechanism. |
| Morales-Garza <i>et al</i> , 2017 <sup>8</sup> | Liver cirrhosis model (CCl <sub>4</sub> ) in <i>Igf1</i> -deficient mice                                | Serum and tissue               | <i>Igf1</i> deficiency exacerbated oxidative stress in the liver, fibrosis and lymphocyte infiltration.                                                                                                                   | Demonstrated that early IGF1 administration could act as a protective factor.                                                                                                 |
| Corea <i>et al</i> , 2016 <sup>9</sup>         | Patients with liver cirrhosis: 138 stable patients and 189 cirrhotic patients with acute decompensation | Serum                          | Reduced serum IGFBP-3 levels in hospitalized cirrhotic patients compared with outpatients and increased after liver transplantation.                                                                                      | Reduced IGFBP-3 were associated with worse prognosis in patients with liver cirrhosis, being a potential biomarker for liver transplantation prognosis.                       |
| Hribal <i>et al</i> , 2013 <sup>10</sup>       | NAFLD subjects: N=221 diagnosed with ultrasonography and N=50 with biopsy                               | Plasma and liver biopsy tissue | In the first cohort, plasma IGF1 were negatively correlated with NAFLD fibrosis and inflammatory biomarkers. In the second cohort, a negative association was also found between NAFLD score and <i>Igf1</i> mRNA levels. | Circulating IGF1 levels could be useful to assess the severity of the disease in NAFLD patients.                                                                              |
| Nishizawa <i>et al</i> , 2012 <sup>11</sup>    | Spontaneous dwarf rat (SDR)/ NAFLD model                                                                | Liver tissue                   | IGF1 administration significantly ameliorates liver fibrosis, steatosis and liver function.                                                                                                                               | Provides proof-of-concept for IGF1 therapy in preventing NAFLD progression.                                                                                                   |
| Blaas <i>et al</i> , 2010 <sup>12</sup>        | Cholestasis mouse model (Mrd2 <sup>-/-</sup> )                                                          | Serum                          | ↓ IGF1 serum levels in mice lacking STAT5. Associated with a down-regulation of hepatoprotective genes.                                                                                                                   | Links the loss of the STAT5 transcription factor to reduced IGF1 and increased susceptibility of liver damage.                                                                |

|                                           |                                                             |                                      |                                                                                                                 |                                                                                                                             |
|-------------------------------------------|-------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| Stefano <i>et al</i> , 2006 <sup>13</sup> | Hepatitis C subjects before (N=34) and after (N=10) therapy | Liver tissue                         | ↑ IGF1R expression in hepatocytes and ↓ <i>Igf1r</i> mRNA content after successful therapy.                     | The increase in IGF1R expression in the liver could constitute a mechanism to stimulate hepatocyte regeneration.            |
| Wang <i>et al</i> , 2003 <sup>14</sup>    | Rat fibrosis model (CCl <sub>4</sub> inhalation)            | Liver tissue                         | ↑ immunoreactive areas for IGF1 and IGF1R correlated with fibrosis development. Reduced by IL10 administration. | IGF1 system is locally activated during fibrogenesis and is responsive to anti-inflammatory modulation (IL10).              |
| Caro <i>et al</i> , 1988 <sup>15</sup>    | Male Sprague-Dawley rats (N=6) and cell culture             | Healthy hepatocytes and HEP-G2 cells | ↑ IGF1 binding sites in hepatocytes from regenerating liver and fetal rat liver.                                | IGF1 binding sites are expressed under physiological conditions indicating their potential use as a pharmacological target. |

The data summarized demonstrates a consistent pattern of systemic IGF1 deficiency coupled with local IGF1R upregulation in hepatic tissue, driving fibrogenesis and inflammation. The table distinguishes between gene expression (mRNA) and protein levels where specified. Abbreviations: CLD, Chronic liver disease; HFD, high fat diet; HSC, hepatic stellate cells; IGF1, Insulin-like Growth Factor 1; IGF1R IGF1 receptor; MASLD/NAFLD, Metabolic dysfunction-associated / non-alcoholic fatty liver disease; MCD, Methionine-Choline Deficient diet; NASH, Non-alcoholic steatohepatitis; SDR, Spontaneous dwarf rat.

Among the several molecular factors that promote the increased polarization of CD4<sup>+</sup> lymphocytes towards Th17, the IGF system is gaining increasing interest. IGF1R expression increases after CD4<sup>+</sup> T cell activation and differentiation toward Th17. Interestingly, this receptor has a unique effect on Th17 cells, increasing IL-17 release and activating Th17 metabolism [41]. Signaling through IGF1R activates aerobic glycolysis, potentiating Th17 differentiation over that of Treg cells [42]. Aerobic glycolysis is the predominant energy pathway in effector T lymphocytes, such as Th17, whereas oxidative phosphorylation predominates in memory T lymphocytes or Treg [43]. Therefore, IGF1R activation could contribute to immune dysregulation and liver damage, favoring Th17 differentiation from naïve CD4<sup>+</sup> T cells. STAT3, as a critical transcription factor for the synthesis and release of the cytokine IL17, is involved in this process [44, 45]. In CLD, the pharmacological inhibition of STAT3 can modulate the balance between Th17 and Treg, shifting it towards Treg with a clear modulatory role of immune activity [46–48]. Similarly, in other settings, the blockade of IGF1Rs has been shown to reduce the phosphorylation of AKT and STAT3 in an *in vitro* model of neuroblastoma [49]. A study conducted by Erlandsson et al (2017) has pointed out that there is an increase in the expression of IGF1R levels in leukocytes of patients associated with systemic inflammation and the inhibition of IGF1R and STAT3 phosphorylation reduces IGF1R receptor levels and significantly ameliorates disease-associated pain, shifting the balance between Th17 and Treg and reducing IL17 levels [50].

Additional studies have shown that the IGF1-IGF1R system is significantly altered in CLD (Table 1). On one hand, chronic tissue injury prompts localized, hyperactivated IGF1R signaling to force activated HSCs into a state of p53/p21-dependent cellular senescence [51,

52]. This specialized cell-cycle arrest shifts their secretome toward a beneficial senescence-associated secretory phenotype (SASP) rich in matrix metalloproteinases (MMPs), which serves as a chemoattractant for immune-mediated clearance, effectively halting progressive liver fibrosis [52, 53]. Conversely, chronic metabolic stress suppresses the functional hepatic GH/IGF1 axis in parenchymal hepatocytes. Due to sustained lipotoxicity and oxidative stress these hepatocytes shift into a toxic senescent state and secrete a destructive SASP loaded with IL-6 and TNF- $\alpha$  [54]. In hepatocytes, an increase in IGF1R receptor expression is observed in pathological conditions, directly altering liver function [55]. In parallel, in the presence of advanced liver fibrosis, the number of healthy hepatocytes capable of producing IGF1 is drastically reduced, contributing to a pro-fibrogenic environment [56]. In this context, IGF1 administration could have a beneficial effect by acting directly on hepatocytes [57, 58].

On the other hand, HSCs play a crucial role in liver fibrogenesis, and regulating their activity could be a key target in the pharmacological modulation of CLD. In this line, IGF1 has also been described as a regulator of HSC activation. Ninjurin2, a protein expressed in hepatocytes, can activate HSCs through IGF1R and increase hepatocyte secretion of fibrogenic cytokines via the IGF1/AKT/STAT3 pathway. Blocking IGF1R activation via a Ninjurin2 antagonist resulted in improved liver function and activity, highlighting the role of IGF1R in disease progression [59]. Conversely, local expression of IGFBP-7 is markedly upregulated in chronic injury, acting as a potent, non-autonomous driver of p53/p21-dependent cellular senescence and expanding the pro-inflammatory SASP [53, 60]. This specific dysregulation characterized by a critical loss of protective circulating IGFBP-3/IGF1 complexes alongside a toxic, localized

accumulation of IGFBP-7 not only compromises peripheral tissue regeneration but also induces systemic effects. By altering remote organ crosstalk, this altered binding protein ratio directly impairs endothelial barriers and neuroglial homeostasis, positioning IGFBPs as pivotal mediators in pathological axes, including the complex bidirectional communication between the dysfunctional liver and the CNS [61, 62].

At clinical level, a study conducted with adolescents diagnosed with MASLD aimed to identify IGF system components as main factors involved in the disease. Gene and protein studies revealed an increase in IGF1R protein expression and *Igf1* gene expression. Interestingly, authors observed an increase in the expression of both in HSCs [63]. Similarly, in adolescents with obesity and histologically diagnosed MASLD, reduced blood levels of IGF1 were observed in those with significant histological damage markers. After multivariate regression, IGF1 and GH levels were associated with liver fibrosis, highlighting the role of these metabolic hormones in liver damage [64]. *Igf1* gene and protein expression were also evaluated in liver samples from adult patients with different MASLD stages. Authors correlated reduced levels of *Igf1* gene expression with increasing severity of MASLD, without changes in IGF1R by immunohistochemistry [65]. Indeed, lower *Igf1* mRNA levels were observed in liver samples from two independent studies including individuals with higher steatosis and MASLD activity scores, and these levels were inversely related to glucose parameters [65, 66]. Interestingly, IGF binding protein levels increased with higher steatosis scores. Similarly, the IGF1-IGF1R pathway is involved in autophagy and pyroptosis in MASH, and lower expression of the long non-coding RNA MIR22HG and IGF1 was also observed in MASH adult patients' liver samples [67].

In experimental models of ACLD induced by both cholestasis and CCl<sub>4</sub>, circulating levels of IGF1 are significantly reduced [68, 69]. Interestingly, in the cholestatic mouse model, lower levels of *Stat5* gene expression, a transcription factor controlling *Igf1* expression, are present in hepatocytes, corroborating the lower serum levels of IGF1 protein in liver cirrhosis. In the CCl<sub>4</sub> model the reduced expression of IGF1 was associated with an increase of IGF1R and activation of the FOXO3a pathway [68, 69]. Similarly, IGF1-deficient mice showed greater vulnerability to CCl<sub>4</sub>-induced liver damage, and lower doses of IGF1 administered for short periods had hepatoprotective, antifibrogenic, and antioxidant effects in a 10-day experimental cirrhosis model [70]. On the contrary, the exploration of the role of the IGF1-IGF1R axis evaluated in cirrhotic rats revealed that signals for both proteins were upregulated during the fibrosis induction period [71]. These results suggest that

the role of the IGF1 ligand could differ depending on the liver disease stage, showing potential upregulation during early stages and a significant decrease at advanced stages.

### The IGF/IGFR system in the liver-brain axis: role in cognition and neuroinflammation in CLD

Beyond hyperammonemia, the pathogenesis of HE in CLD is related to the disruption of the gut-liver-brain axis. In patients with advanced cirrhosis, portal hypertension and altered mucosal immunity induce gut dysbiosis characterized by an overgrowth of pathogenic taxa and the reduction in short-chain fatty acid (SCFA)-producing bacteria [72]. This dysbiosis compromises the integrity of intestinal tight junctions, leading to a "leaky gut" and driving pathological bacterial translocation. Consequently, viable bacteria and pathogen-associated molecular patterns (PAMPs) leak into the portal circulation. In the liver, these microbial products fail to be cleared due to parenchymal dysfunction and portosystemic shunts, spilling into the systemic bloodstream and triggering cirrhosis-associated immune dysfunction (CAID). Once in the systemic circulation, these microbiota-derived inflammatory mediators stimulate the production of pro-inflammatory cytokines. Up to 80% of patients with cirrhosis exhibit mild neurocognitive dysfunction. This condition, termed minimal or covert HE (CHE), significantly impairs quality of life [73] and serves as a clinical predictor for the onset of overt HE [74]. Common precipitating factors for these episodes include gastrointestinal bleeding, electrolyte imbalances, infection, and the use of diuretics [75]. Broadly, HE encompasses a spectrum of cognitive, psychomotor, and psychiatric disturbances that signal a poor prognosis, negatively affecting survival rates, liver transplant priority, and overall health-related quality of life [76]. Notably, cirrhotic patients face a higher risk of falls and severe injuries, such as intracranial hemorrhages or pelvic fractures, with HE acting as an independent risk factor for these complications [77].

From a neurological perspective, the HE observed in cirrhosis is primarily astroglial in nature. It is characterized by Alzheimer type 2 astrocytosis and microglial activation, which indicates underlying neuroinflammation [78, 79]. The synergy between systemic inflammation and hyperammonemia is a central driver of cognitive impairment [80]; research suggests that inflammation works alongside ammonia to promote the nitrosation of brain proteins and alter BBB permeability [81–83]. Through the disruption of endothelial tight junctions and the activation of specific endothelial receptors, circulating cytokines and PAMPs gain access to the central nervous system. This microenvironment triggers microglial activation and

reactive astrocyte hypertrophy (astrocyte swelling), culminating in profound neuroinflammation, oxidative stress, and neural dysfunction, which ultimately accelerates the onset and severity of cognitive deficits in HE [84]. Clinically, elevated levels of pro-inflammatory cytokines are observed in patients with CHE [85]; in cases of extrahepatic portal venous obstruction, these mediators correlate directly with serum ammonia levels [86]. The pathogenic role of the neutrophil response is also well-documented [87], with specific mediators like IL-1 $\beta$  and IL-6 correlating closely with both neurocognitive scores and quality-of-life metrics [88].

Recent studies highlight the involvement of Th17 cells in cognitive impairment. These cells can breach the BBB and exacerbate brain injury in various neurological disorders [89]. In the context of advanced liver disease, the systemic inflammation inherent to cirrhosis may increase the permeability of the BBB, facilitating the recruitment of T cells into the CNS and further driving neurodegeneration [90].

IGF1 acts as a key upstream regulator of this immunological checkpoint. In the setting of CLD, the mechanisms governing BBB breach by peripheral Th17 cells are highly distinct from classic autoimmune demyelinating pathologies, avoiding broad generalizations. Hepatic dysfunction triggers a unique systemic cascade characterized by the accumulation of neurotoxins such as ammonia and circulating bile acids, alongside a critical decline in liver-derived endocrine factors, most notably IGF1 [91, 92]. Circulating IGF1 normally exerts a powerful stabilizing effect on the cerebral endothelium, maintaining the architectural integrity of tight junction proteins like claudin-5 and occludin via the AKT/mTOR pathway [93]. When hepatic IGF1 synthesis fails during ACLD, the compromised cerebral endothelium becomes highly susceptible to elevated systemic levels of IL-17 and TNF- $\alpha$  [94]. The upregulation of cell adhesion molecules facilitates the targeted infiltration of peripheral Th17 cells into the CNS parenchyma, which directly initiates downstream neuroinflammatory cascades within the brain [95, 96]. Upon sensing Th17-derived cytokines (IL-17 and IL-22), microglia activation initiates a potent cellular crosstalk, releasing a specialized cocktail of cytokines, including IL-1 $\beta$  and TNF- $\alpha$ , which cooperatively drive neighboring astrocytes toward a neurotoxic, reactive A1 phenotype [97]. In addition, this glial-immune cell network is tightly modulated by localized trophic networks, where microglial-derived IGF1 serves as an essential autocrine and paracrine brake. Under physiological conditions, locally synthesized IGF1 promotes astrocyte survival, restrains microglial overactivation, and preserves the homeostatic glutamate-uptake capacity of astrocytes [98]. However, under the chronic input of Th17-derived signals

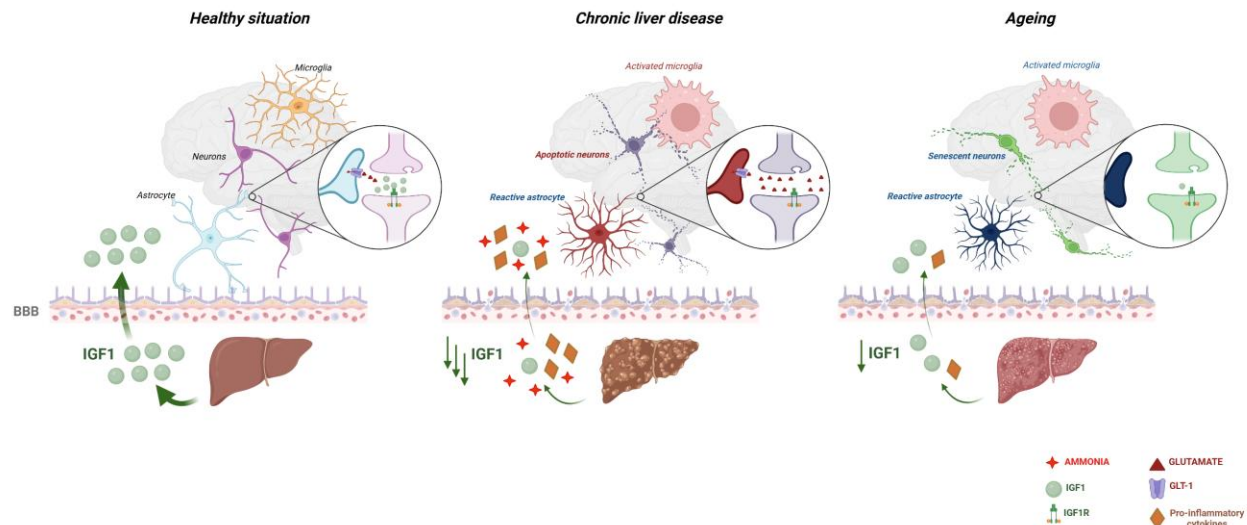
and systemic hepatic toxins, the local downregulation of IGF1 signaling cascades dismantles this protective loop, compounding the pro-inflammatory feedback cycle between microglia and astrocytes [99]. Therefore, neuroinflammation in CLD represents a complex dysregulation of the intricate crosstalk connecting infiltrating Th17 cells, microglia, and astrocytes, where the loss of protective IGF1 signaling within this glial triad shifts the CNS environment toward sustained, self-propagating neurodegeneration [100].

The interaction between IGF1/IGF1R signaling and the SASP regulates tissue remodeling, chronic sterile inflammation, and structural aging [51, 101]. This pathway exerts highly specific pathophysiological outcomes across the hepatic and cerebral microenvironments [51]. IGF1, acting as a growth factor, is also involved in the protein synthesis necessary for the growth and survival of different cell populations of the brain, such as neurons, astrocytes, Schwann cells, and microglia [102]. The IGF1 ligand and its corresponding receptor in the brain are not only key regulators of cellular metabolism but are also highly involved in cognitive decline and memory (Fig. 2). Under physiological conditions, IGF1 is crucial in modulating inflammation in neurons and glia, promoting myelination, and maintaining a balance in astrocyte functions and neuronal synaptogenesis, both early in life and in adulthood [103–105]. Additionally, IGF1 has been shown to enhance neurogenesis in the dentate gyrus of the hippocampus, one of the few brain regions with active neurogenesis involved in memory and cognition [106].

Astrocytes are the predominant cells in the brain with a key role in neurogenesis and synaptogenesis, modulating the availability of glutamate—the main neurotransmitter with excitatory actions and potential neurotoxic effects—and exhibiting neuroprotective actions [107]. The role of IGF1 at this level appears twofold. On the one hand, IGF1 is involved in the expression of a membrane transporter responsible for glutamate uptake by astrocytes [108]. On the other hand, IGF1 mediates oxidation-reduction processes in cells, protecting them from damage induced by reactive oxygen species [109–111]. All these cellular effects have been linked to the neuroprotective and pro-cognitive actions of IGF1 in different animal models [109]. Clinical and biological changes associated with HE induce brain alterations that affect fundamental cell morphology and function. Increased ammonia, systemic inflammation, and elevated metabolite levels in plasma induce metabolic and oxidative stress, negatively impacting brain health and driving neuroinflammation. To track the neuroinflammatory consequences of peripheral growth factor deficiency, fluid-based biomarkers reflecting glial activation and structural neuronal damage offer

significant translational utility. Glial fibrillary acidic protein (GFAP) and S100B, both clinical markers of reactive astrogliosis and astrocyte injury, are elevated in response to hyperammonemia and central IGF1 signaling failure [112, 113]. Furthermore, neurofilament light chain (NFL), a highly stable biomarker released into the blood and cerebrospinal fluid (CSF) during axonal degradation, can serve as a proxy for the structural neurodegeneration that follows chronic microglial activation and endothelial dysfunction [114, 115]. The exposure of astrocytes to this toxic environment alters their cellular microstructure, specifically modifying the expression of intermediate filaments such as GFAP, which are essential for motility

and structural stability in these cells [116]. Interestingly, these changes are more prominent in the hippocampus, a brain region critically involved in memory and cognition. Brain edema induced by HE could be one of the main factors contributing to GFAP reduction, as previously described [117]. Furthermore, astrocytes are considered the primary target of ammonia toxicity, as they are responsible for ammonia metabolism via the glutamine synthetase enzyme expressed within these cells [118, 119]. In HE, astrocytes experience an increase in intracellular glutamine concentrations driven by circulating ammonia, leading to a hyperosmotic state, water accumulation, and cytotoxic astrocyte swelling.



**Figure 2. Central role of liver-derived IGF1 and systemic factors in maintaining brain homeostasis and their disruption in pathological states.** (Left) Healthy situation: A healthy liver secretes adequate levels of IGF1, which crosses the intact blood-brain barrier (BBB), exerting neuroprotective effects. Astrocytes maintain physiological glutamate clearance via the GLT-1 transporter, supporting normal neuronal and microglial function. (Middle) Chronic liver disease: In advanced cirrhosis, liver damage induces a drastic reduction in circulating IGF1 levels, alongside a significant increase in ammonia and pro-inflammatory cytokines. These systemic alterations disrupt the BBB, promoting a neurotoxic environment. Consequently, microglia become activated and astrocytes acquire a reactive phenotype, reducing GLT-1 expression. This impairment induces glutamate accumulation in the synaptic cleft, ultimately leading to excitotoxicity and neuronal apoptosis. (Right) Aging: Similarly, the aging process is correlated with a progressive decline in liver-derived IGF1 and the presence of low-grade systemic inflammation. The loss of IGF1 neurotrophic support, combined with the infiltration of pro-inflammatory cytokines, induces microglial activation, astrocyte reactivity, and neuronal senescence, driving the cognitive decline associated with accelerated aging.

Microglia, the brain's main resident macrophages, are the predominant immune cells in the healthy brain and are involved in neuronal protection under physiological conditions. However, activated microglia can induce neuronal death by increasing oxidative stress and glutamate release, while decreasing nutritive and neuroprotective brain-derived neurotrophic factor (BDNF) and IGF1 [120]. Under healthy physiological conditions, robust microglial IGF1R activation suppresses NF- $\kappa$ B activation, securing an anti-inflammatory, neuroprotective, pro-resolving state [121]. *In vitro* studies have indicated that IGF1 secreted by microglia acts as a trophic factor in the brain microenvironment, essential for

neuronal survival and growth, especially in the early stages of life [122]. Thus, IGF1 administration could promote microglia differentiation towards the M2 phenotype, which exerts an anti-inflammatory and protective role that is normally reduced in pathological situations involving chronic inflammation [123]. Microglial cells are involved in neuroinflammation associated with several neurological and psychiatric disorders. Evidence of microglial activation has been demonstrated in patients with HE, as well as in those with acute and chronic liver failure. During chronological aging and advanced organ failure, local and blood-borne IGF1 supplies drop sharply, triggering premature glial

senescence [121, 124, 125]. The senescent microglia and astrocytes unleash an intense neurotoxic SASP (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ) that breaks down synaptic connectivity [121, 124]. This persistent glial-derived inflammatory environment activates downstream stress kinases that block insulin receptor substrates (IRS-1/2), inducing local brain IGF1 resistance and locking the CNS into a self-perpetuating cycle where chronic inflammation prevents cellular repair and accelerates neurodegeneration [121]. Furthermore, postmortem brain studies have also revealed an increase in the microglial marker IBA1 in cirrhotic patients with HE [126]. Although ammonia stimulates microglial activation of STAT3 and the secretion of IL-6 in culture media, these *in vitro* findings were not corroborated in an animal model of oral ammonia exposure [100, 127]. Interestingly, hyperammonemia has been associated with cognitive decline in mice, which was successfully reversed following anti-TNF- $\alpha$  treatment [100].

The impact of IGF1 on crucial brain cell populations translates into the relevance of the IGF1-IGF1R axis on cognition. In a model of spinal cord injury with neuroinflammation, impaired hippocampal neuroplasticity, and cognitive impairment, IGF1 administration improved not only cognitive deficits in the Y-maze and novel object recognition (NOR) tests but also microglial activation in the hippocampus [128]. In an animal model of Alzheimer's disease, reduced hippocampal levels of IGF1 and BDNF were found alongside memory impairment, which improved with exercise exposure and insulin treatment [129]. Central intracerebroventricular IGF1 administration protected working memory in the Morris water maze test and reduced hippocampal microglia activation in a sporadic model of the disease in rats [130]. Similar effects were found in a model of Parkinson's disease, showing that adenovirus-induced IGF1 overexpression in the dorsal hippocampus improved cognitive deficits related to spatial and working memory in the Y-maze and novel location recognition tests, reversing dopaminergic damage induced by the model [131]. Chronic pain was also associated with cognitive impairment, reduced IGF1 levels, and an impaired PI3K/AKT pathway in the dentate gyrus of the hippocampus in mice. In this model, An et al. demonstrated that direct IGF1 administration significantly improved cognitive deficits via the AKT pathway, restoring neurogenesis and cell excitability in this brain region [132]. In an animal model of ischemia, IGF1 administration reduced BBB permeability, showing neuroprotective actions in aging brain [133]. Age-related BBB disruption could also be correlated with IGF1 decline inducing endothelial senescence, increasing the vulnerability to intracerebral hemorrhages [134]. Here, IGF1 administration to intracerebral hemorrhages

presenting mice demonstrated its neuroprotective effects, reducing edema, BBB permeability, and improving revascularization and behavioral alterations [135–137].

Clinical studies have also pointed out the correlation between IGF1 plasma levels and cognitive abilities. These studies indicate an inverse relationship between plasma levels of IGF1 and cognitive impairment in patients with established neurological disease, such that lower plasma or serum levels of the ligand are associated with higher cognitive decline [138]. Interestingly, similar results are observed in patients with mild cognitive impairment, a common clinical condition in diseases that may have a systemic cause, such as diabetes [139, 140]. On the other hand, increased plasma levels of IGF1 could be related to cognitive improvement and a reduction in peripheral inflammation [141].

In rodents, depressive-like alterations were evaluated following subacute and chronic CCl<sub>4</sub> administration. Subacute CCl<sub>4</sub> administration induced depressive-like behaviors in both the tail suspension and sucrose preference tests, highlighting the emotional alterations associated with this 23-day treatment protocol [142]. Similarly, a study conducted by our group demonstrated increased anxiety-like behaviors in young and old mice exposed to CCl<sub>4</sub>-induced liver injury, alongside significant cognitive impairments in the NOR test [143]. These results underscore the impact of liver damage at the central level, driving emotional and cognitive disturbances associated with the disease.

### Modulation of the IGF/IGFR system during aging

IGF1 hormone has been proposed as an age-related marker with a significant impact on lifespan and quality of life. IGF1 axis mutations have been associated with changes in lifespan, and several studies have reported that circulating IGF1 levels decrease with age. The maintenance of muscle mass in young rats, for instance, is dependent on GH and IGF1, both of which exhibit reduced circulating levels with age [144]. However, the role of IGF1 is highly paradoxical. While increased IGF1 levels protect the musculoskeletal system, they have also been associated with increased oxidative stress and mortality [145]. Furthermore, there is a notable difference between rodents and humans: whereas in rodents, serum levels of IGF1 remain high throughout life, humans experience a distinct decrease during aging.

Exploring this balance, researchers found that the deletion of the *Igf1* gene at one year of age reduces serum IGF1 levels by 70% and dramatically impairs lifespan. Reduced serum levels of IGF1 have been associated with higher GH levels, increased liver weight, inflammation, and oxidative stress. Therefore, despite increased GH levels, reduced IGF1 concentrations impaired health and

lifespan, thereby increasing liver tumor incidence [146]. This critical dynamic was further demonstrated in a mouse model of accelerated aging (mice lacking *Zmpste24* metalloproteinase), where a drastic reduction in plasma IGF1 levels was observed alongside higher GH levels. Treatment with recombinant IGF1 restored the balance between GH and IGF1, increased lifespan, and delayed the onset of several functional alterations [147]. Additionally, IGF1 involvement in aging was evaluated using a genetic animal model of accelerated aging, *Xpd*<sup>T<sup>TD</sup></sup> mice. In this model, investigators observed a reduction in hepatic IGF1-mediated signaling—considered a major regulator of lifespan—along with an increased apoptotic response [148].

The age-related decline in IGF1 is also closely linked to metabolic regulation and dietary factors. Decreased IGF1 levels observed in aging are strongly associated with increased levels of phosphorylated FOXO. Interestingly, dietary restriction normalizes IGF1 levels in old mice, modulating FOXO phosphorylation and exerting neuroprotective effects [149, 150]. Calorie restriction (CR) has significant effects on circulating IGF1 levels; after 3 months of CR, mice exhibited reduced circulating IGF1 levels, which positively impacted glucose tolerance and insulin resistance while attenuating oxidative damage. Conversely, none of these beneficial changes were observed in protein-restricted animals [151]. Alongside the ligand, modulation of the IGF1R presents valuable therapeutic avenues. The deletion or blockade of IGF1R has been correlated with improvements in aging-related and metabolic alterations. Middle-aged mice with IGF1R deficiency were able to counteract the negative effects of aging and a high-fat diet on glucose metabolism and inflammation [152]. This peripheral growth factor deficiency drives neurovascular aging. At the BBB interface, compromised endothelial IGF1R signaling accelerates the senescence of cerebrovascular endothelial cells and astrocytes, disrupting tight junctions and compromising barrier integrity [101, 153]. This systemic breach delivers peripheral inflammatory signals and neurotoxic metabolites directly to the central nervous system, driving secondary neuroglial senescence and solidifying a destructive axis of aging between the failing liver and the brain [101, 154].

Communication within the liver-brain axis is critical to understanding the neurological decline associated with aging. In this context, CLD induces more severe clinical complications in aging patients, where hyperammonemia and chronic inflammation synergistically induce neurotoxicity, astrocyte senescence, and cognitive alterations [91]. Interestingly, the IGF1/IGF1R signaling system plays a central role in this process, presenting a complex paradox where its effects diverge based on the specific tissue context and disease stage [101]. The

progressive decline in circulating IGF1 levels induced by liver damage has a negative impact on the hepatic inflammatory balance between Th17 and Treg cells, and on the central nervous system, reducing neurotrophic support and promoting reactive astrogliosis and cerebrovascular alterations [121, 153] (Fig. 2). However, while a systemic reduction is often viewed as a protective hallmark of longevity, the resulting local deficiency or resistance within specific microenvironments has proven highly deleterious, accelerating organ-specific structural aging [101, 155, 156].

In the liver specifically, the activation via the IGF1 ligand enhances cell longevity and reduces liver fibrosis. As described previously, liver fibrosis is characterized by a decrease in plasma IGF1 levels. The intrahepatic overexpression of the *Igf1* gene modulates hepatocyte oxidative stress and premature senescence in a model of liver cirrhosis. In addition, the exogenous administration of IGF1 achieves the same positive outcomes, highlighting the protective role of the ligand against cellular senescence induced by CCl<sub>4</sub> administration in rats [157]. Conversely, some models highlight that IGF1 deficiency can be protective under specific aging conditions. One study correlated IGF1 deficiency with lifespan extension and less pronounced liver alterations associated with aging. Specifically, in IGF1-deficient mice, aging-associated elevations in triglycerides, AST, and ALT, as well as steatosis and fibrosis, were significantly attenuated in the liver, likely by preventing deleterious autophagic processes [158]. These discrepancies might be related to the constitutive deficiency of the IGF1, potentially inducing physiological mechanisms to compensate for this lack of signaling.

Beyond hepatic health, the blockade of IGF1R has been associated with ameliorated neuroinflammation in a mouse model of Alzheimer's disease [159]. In insulin-resistant aged rats, central IGF1 treatment improved general insulin resistance and suppressed hepatic glucose production, suggesting that both central and peripheral levels of IGF1 should be considered to optimize its use as a pharmacological target [160]. Systemic IGF1 deficiency also severely compromises cerebrovascular health. Liver-specific IGF1 knockdown has been associated with decreased vascular resistance to oxidative stress. Using Cre-lox technology, researchers reported that targeted IGF1 deficiency reduces circulating IGF1 levels by approximately 50%, inducing vascular dysfunction and an antioxidant-deficient response [161]. Consequently, mice lacking hepatic IGF1 showed an early onset and increased incidence of cerebral microhemorrhages and associated behavioral and cellular alterations, positioning IGF1 as a promising protective factor against cerebrovascular accidents [162]. Furthermore, the age-related decline in circulating IGF1 promotes the pathogenesis of

intracerebral hemorrhages, contributing to the development of vascular cognitive impairment [163]. Beyond cognitive and vascular decline, the impact of IGF1 deficiency in the liver and hippocampus extends to mood disorders. The absence of the *Igf1* gene in both the liver and hippocampus induced depressive-like behaviors in mice, leading to the conclusion that age-induced IGF1 deficiency alone is sufficient to trigger these behavioral changes [2]. Consequently, according to hepatic and extrahepatic evidence, the modulation of the IGF1/IGF1R axis emerges as a promising pharmacological target in aging research [101].

### Translational perspective and clinical implications

Emerging clinical and preclinical evidence indicates that biological sex acts as a critical determinant in the susceptibility to, and progression of liver-disease-associated neurocognitive impairment, mediated by distinct dimorphisms in both the IGF system and immune reactivity. Sexual dimorphism in the GH-IGF1 axis is well-established; males typically exhibit pulsatile GH secretion patterns resulting in distinct peaks of hepatic IGF1 synthesis, whereas females display a more continuous, tonic GH secretion [164]. Crucially, estrogens exercise profound regulatory control over this system by modulating hepatic IGF1 transcription and enhancing central IGF1R sensitivity [165, 166]. The age-associated decline in estrogen levels during menopause abruptly strips females of this neuroprotective buffer, rendering the aging female brain disproportionately vulnerable to the consequences of peripheral IGF1 deficiency [167]. Simultaneously, the immune response underlying the liver-brain axis displays marked sex-specific polarization. Females generally mount a more robust innate and adaptive immune response, which, in the context of CLD, can accelerate Th17 cell differentiation and subsequent breach of the BBB [168]. However, microglia exhibit highly distinct sex-specific transcriptomic profiles and morphological trajectories during aging. While young females benefit from estrogen-mediated suppression of microglial activation, senescent or post-menopausal females exhibit a hyper-reactive, "primed" microglial phenotype that responds more aggressively to peripheral inflammatory insults, such as Th17 infiltration or hyperammonemia, compared to age-matched males [169]. In contrast, males facing CLD demonstrate a higher baseline vulnerability to early endothelial cerebrovascular damage and oxidative stress under IGF1-deficient conditions [170, 171]. Acknowledging these sex-specific trajectories is paramount, as the molecular mechanisms driving neurocognitive decline shift fundamentally based on the patient's hormonal and chromosomal landscape.

The clinical translation of the liver-brain axis framework requires the validation of robust, minimally invasive biomarkers capable of monitoring peripheral hepatic dysfunction, BBB degradation, and central neuroinflammation. Because circulating total IGF1 levels often fluctuate based on age, nutritional status, and the stage of CLD, monitoring total ligand concentration alone is insufficient. Instead, a comprehensive biomarker panel must evaluate the bioavailability of IGF1 by quantifying the ratio of free-to-bound IGF1 alongside specific binding proteins, particularly IGFBP-1 and IGFBP-3, which serve as highly sensitive indicators of altered hepatic growth factor synthesis and systemic insulin resistance [172, 173]. From the immunological perspective, tracking the peripheral polarization and central infiltration of the adaptive immune system is paramount. Quantifying circulating IL-17A levels, alongside the longitudinal tracking of the Th17/Treg ratio via flow cytometry, provides a direct readout of the systemic pro-inflammatory drive capable of compromising BBB tight junctions [174]. This can be combined with vascular endothelial biomarkers, such as soluble vascular cell adhesion molecule-1 (sVCAM-1) and matrix metalloproteinase-9 (MMP-9), to non-invasively assess the rate of cerebrovascular remodeling and barrier breach [175, 176].

This peripheral metabolic profile must be coupled with fluid and neuroimaging biomarkers of central neurodegeneration, including plasma NFL to gauge ongoing axonal injury, plasma GFAP to detect reactive astrogliosis, muscle-derived irisin to track the compounding effects of sarcopenia, and translocator protein (TSPO)-PET imaging to directly visualize microglial activation in vivo [177]. Proton magnetic resonance spectroscopy (MRS) allows for the precise, non-invasive quantification of central metabolic shifts, specifically tracking elevations in the glutamine/glutamate peak—a direct consequence of hyperammonemia—alongside decreases in myo-inositol, which indicates osmoregulatory failure in astrocytes. When coupled with diffusion tensor imaging (DTI) to monitor microstructural white matter changes, this multimodal biomarker framework empowers clinicians to track disease progression, stratify patient risk, and objectively evaluate the efficacy of future IGF-targeted or anti-inflammatory therapeutic interventions [95, 178, 179].

The pharmacological targeting of the liver-brain axis via IGF1 modulation represents a therapeutic challenge; however, these strategies must navigate significant clinical risks, including detrimental systemic metabolic alterations and the potential oncogenic implications of over-activating a potent mitogenic pathway in premalignant or fibrotic tissues [53, 180]. Preclinical

evidence using rodent models such as the high-fat high-fructose (HFHF) diet to simulate progressive MASLD/MASH or the azoxymethane-induced model of acute liver failure demonstrates that administering recombinant human IGF1 (rhIGF1) or its co-formulation with IGFBP-3 successfully blocks hepatic fibrosis, preserves hippocampal synaptic plasticity, and blunts microglial neuroinflammation [82, 181]. However, human clinical trials evaluating systemic rhIGF1 have faced severe setbacks due to an exceptionally short circulating half-life and dangerous adverse profiles, most notably profound hypoglycemia driven by IGF1 cross activating the insulin receptor at therapeutic concentrations [182]. Proposing IGF1/IGF1R modulation as a definitive clinical therapy remains premature without overcoming major physiological constraints, such as rapid receptor desensitization and critical dosage toxicities in elderly populations, who are prone to drug accumulation, fluid retention, and eccentric myocardial hypertrophy [183].

### Future directions

As shown in this review, IGF1 serves as a critical systemic mediator maintaining the functional integrity of the liver-brain axis. CLD and advanced aging share a convergent pathophysiological pathway characterized by a severe decline in circulating IGF1, which exacerbates BBB disruption, neuroinflammation, and astrocytic dysfunction. This loss of neurotrophic and immunological support drives the progression of neurocognitive complications, such as HE and accelerated cognitive decline. Consequently, restoring IGF1 signaling represents a promising therapeutic strategy to mitigate neurodegeneration and improve cognitive health in patients with advanced CLD.

Future research should focus on clarifying the stage-dependent role of the IGF/IGFR system during CLD progression to determine the precise therapeutic window for recombinant IGF1 administration. Additionally, further mechanistic studies are needed to elucidate the exact molecular pathways by which peripheral hepatic growth factor deficiencies trigger endothelial senescence and compromise BBB tight junctions. Investigating the specific immune-glial crosstalk—particularly how diminished IGF1 signaling drives Th17 cell infiltration and shifts microglia toward neurotoxic phenotypes—will be crucial. Finally, evaluating fluid-based biomarkers like GFAP, S100B, and NFL in clinical trials could provide reliable translational tools to track neuroinflammation, validate targeted therapies, and ultimately mitigate the synergistic effects of advanced aging and HE on cognitive decline. To address this clinical gap moving forward, future efforts should focus on validating an integrated

multimodal framework combining these IGF-related and neuroglial markers with advanced neuroimaging measures. Establishing such a standardized, comprehensive panel will be critical for diagnosing early neurocognitive impairment and predicting disease progression in CLD.

### Funding

This study was supported by Generalitat Valenciana, Valencia, Spain, under the grant CIPROM 2024/0019, by Instituto de Salud Carlos III, Madrid, Spain, under the grant PMP21/0082, by Agencia Estatal de Investigación, Madrid, Spain, under the grant PID2023-149765OB-I00 available to RF, and by Navarro-Tripodi Foundation, under the grant Navarro-Tripodi-2024 available to EC and AG.

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