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Review

Growth hormone as a treatment for post-stroke recovery: a review of preclinical and clinical evidence

Emmanuelle Zakheim, Daniel Moon, Wesley Tran, Ephrem Gerald and Mohamed Ahmed*

Department of Basic Sciences, College of Medicine, California Northstate University, West Taron Drive, Elk Grove, CA 95757 USA

* **Correspondence:** Email: mohamed.ahmed@cnsu.edu.

Abstract: Despite advances in acute stroke management, many survivors experience lasting motor and cognitive long-term sequelae. Acute reperfusion therapies and prevention strategies are well established, but options to enhance long-term motor and cognitive recovery remain limited. Several pharmacologic adjuncts (selective serotonin reuptake inhibitors (SSRIs), cholinesterase inhibitors, memantine) have shown inconsistent efficacy or safety, highlighting an unmet need for effective post-stroke recovery therapies. Growth hormone (GH) has emerged as a candidate adjunctive therapy based on its neurotrophic properties and the discovery of an endogenously activated neural GH axis following brain injury. This review aims to summarize GH's proposed mechanisms to promote neurorecovery after a stroke and to synthesize preclinical and clinical evidence supporting its use as an adjunct to standard post-stroke rehabilitation. A narrative review of preclinical and clinical studies that examined GH administration following ischemic stroke was conducted, emphasizing functional, cognitive, and safety outcomes; mechanistic findings connecting GH to neurotrophic signaling, synaptic plasticity, and cerebrovascular remodeling are also discussed. Preclinical studies demonstrated that GH administration after a stroke accelerates motor recovery, improves spatial and associative memory, reduces peri-infarct tissue loss, and increases neurotrophic, synaptic, and angiogenic markers (BDNF, IGF-1, VEGF). Four human clinical trials, along with the phase I-II COURAGE trial of GH-secretagogue therapy, reported significant improvements in functional independence (Korean Modified Barthel Index (K-MBI), motor and cognitive scores (Fugl-Meyer, Montreal Cognitive Assessment), and reduced neurological deficit (Modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS) in GH-treated patients compared with controls, without serious adverse events. Preclinical and early clinical evidence supports GH as a promising and safe adjunct to standard post-stroke rehabilitation, particularly for enhancing motor and cognitive

recovery; however, existing clinical trials are small and varied in design, and larger, multicenter randomized controlled trials are required to establish optimal dosing, timing, and treatment duration before GH can be incorporated into standard post-stroke care.

Keywords: recombinant human growth hormone; stroke rehabilitation; neuroregeneration; neuroplasticity; functional recovery; neuroprotection; ischemic stroke

Abbreviations: ALFF: Amplitude of Low-Frequency Fluctuations; BBB: Blood-Brain Barrier; BDNF: Brain-Derived Neurotrophic Factor; BID: Bis In Die (twice daily); BOLD: Blood-Oxygen-Level-Dependent; BrdU: Bromodeoxyuridine; BUN: Blood Urea Nitrogen; CBC: Complete Blood Count; CD31: Cluster of Differentiation 31; CT: Computed Tomography; DCX: Doublecortin; DEXA: Dual-Energy X-ray Absorptiometry; DMN: Default Mode Network; EGF: Epidermal Growth Factor; ET-1: Endothelin-1; FAC: Functional Ambulation Category; FC: Functional Connectivity; FMA: Fugl-Meyer Assessment; fMRI: Functional Magnetic Resonance Imaging; GH: Growth Hormone; GH3: Growth Hormone, 3-month treatment group; GH6: Growth Hormone, 6-month treatment group; GHR: Growth Hormone Receptor; GHRP-6: Growth Hormone-Releasing Peptide 6 (Growth Hormone-Releasing Hexapeptide); HbA1c: Hemoglobin A1c; ICV: Intracerebroventricular; IGF-1: Insulin-like Growth Factor-1; IV: Intravenous; K-MBI: Korean Modified Barthel Index; K-MMSE: Korean Mini-Mental State Examination; LDL(-C): Low-Density Lipoprotein (Cholesterol); MBP: Myelin Basic Protein; MI: Motricity Index; MMT: Manual Muscle Test/Strength; MoCA: Montreal Cognitive Assessment; mRS: Modified Rankin Scale; mTOR: Mechanistic (Mammalian) Target of Rapamycin; NeuN: Neuronal Nuclei (neuronal marker); NIHSS: National Institutes of Health Stroke Scale; NS: Not Significant; OR: Odds Ratio; p70S6K: p70 S6 Kinase; PAL: Paired-Associate Learning (task); PSD-95: Postsynaptic Density Protein 95; RCT: Randomized Controlled Trial; rhGH: Recombinant Human Growth Hormone; rTMS: Repetitive Transcranial Magnetic Stimulation; SAE(s): Serious Adverse Event(s); SC: Subcutaneous; SVZ: Subventricular Zone; SYN-1: Synapsin-1; tDCS: Transcranial Direct Current Stimulation; TBI: Traumatic Brain Injury; TG: Triglycerides; VA/DoD: Veterans Affairs/Department of Defense; VEGF: Vascular Endothelial Growth Factor

1. Introduction

Stroke continues to be one of the leading causes of death and disability adjusted life years both globally and in the United States [1]. Patients face severe decreases in their quality of life for years post-stroke with many functional impairments becoming permanent. Because there is no agreed upon standard stroke recovery timeframe, this review distinguishes stroke recovery according to the temporal phase and the specific time from stroke onset is reported when describing individual studies whenever available. When not available, the acute phase will encompass the initial period following the stroke, during which stabilization and reperfusion therapies are prioritized; in contrast to how the subacute or chronic phases are when rehabilitation, long term recovery and possible persistent deficits dominate.

The treatment of an acute ischemic stroke has three primary domains: acute management, long-term rehabilitation, and secondary prevention. Acute management centers on a time-dependent reperfusion therapy, with the two pillars being thrombolysis and mechanical thrombectomy [2]. These treatments aim to mitigate neural ischemia and prevent mortality but are limited in terms of long-term

rehabilitation. Additionally, many patients are not even eligible for these treatments as they either do not meet the time frame criteria or have secondary co-morbidities that preclude treatment [3]. This leaves a significant portion of the population already at a disadvantage due to their inability to receive recanalization therapy, further validating the need for more therapeutic options targeted at neuro-recovery. Secondary prevention involves antithrombotic therapy, blood pressure control, management of dyslipidemias, and lifestyle modifications. This does not affect a patient's ability to regain lost cognitive functioning but prophylactically reduces future stroke incidence. Once stable, long-term motor and cognitive recovery require complex utilization of multidisciplinary approaches [4–6].

Post-stroke rehabilitation should begin as soon as the patient is medically stable and addresses multiple interconnected domains. According to the American Heart Association, American Stroke Association, Veteran Affairs (VA), and Department of Defense (DoD) guidelines, the major domains include motor therapy, dysphagia management, cognitive and speech therapy, mental health treatment, and community reintegration [7,8]. Motor strength and mobility recovery, the most extensively studied domain, has largely been addressed via physical rehabilitation including, but not limited to, task-specific repetitive training, constraint-induced movement therapy, cardiovascular/aerobic exercise, progressively challenging functional practices, and functional electrical stimulation [8]. While physical rehabilitation has shown a great benefit to many patients, it requires high levels of adherence. This can be difficult for many post-stroke patients, who often face difficulties with increased fatigue, depression, and anxiety [9]. Offering pharmaceutical options, in conjunction with physical rehabilitation, may help improve motor recovery at a faster rate, thus reducing the mental burden and increasing compliance.

Similar to motor recovery, cognitive recovery centers around focused rehabilitation and learning compensatory strategies [10]. Examples include strategy and computerized cognitive training [11]. Similar to motor rehabilitation, cognitive rehabilitation requires intense patient commitment for improved results. Additionally, non-invasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have emerged as potential effective adjuncts to the standard rehabilitation therapy [12,13]. Unfortunately, due to potential adverse effects, the 2024 VA/DoD Stroke Rehabilitation Guideline concluded that there was insufficient evidence to recommend for or against either technique in stroke rehabilitation [14].

Various pharmacotherapy options for post-stroke recovery have been studied. Recombinant human growth hormone (rhGH) treatment has emerged as a potential investigational adjunct therapy to enhance the post-stroke neurologic recovery [15]. Its use in animal and human models has demonstrated improved neurologic outcomes across a variety of domains with a generally high safety profile [16,17]. This review aims to address the possible mechanisms of action of rhGH on functional neurologic improvement in post-stroke patients as well as consolidate evidence of its use as a potential adjunct therapy that could improve patient outcomes when used in conjunction with traditional post-stroke therapies such as physical therapy and cognitive therapy.

Other pharmaceutical therapies have been trialed but have shown little efficacy and safety in post-stroke rehabilitation. In a meta-review of over 76 randomized controlled trials utilizing selective serotonin reuptake inhibitors (SSRIs), there was significant evidence that this drug class did not benefit in terms of post-stroke disability or independence compared to a placebo or usual care [18]. Cholinesterase inhibitors have shown some evidence of improvement in dementia post-stroke, but randomized controlled trials have shown inconsistent efficacy and possible serious adverse effects [19]. Similarly, a meta-analysis found that memantine, an N-Methyl-D-aspartic acid (NMDA) receptor

antagonist, was shown to have efficacy in enhancing cognitive functions across multiple randomized controlled trials, but included various patient etiologies on cognitive impairment, leading to uncertainty regarding memantine's utilization specifically post-stroke [18]. With many of the current pharmacological treatments for post-stroke recovery having flaws, rhGH therapy is a potential treatment option that can fill in the niche for post-stroke rehabilitation.

2. Growth Hormone biology and background

Growth Hormone (GH) is produced in the body by the somatotropic cells of the anterior pituitary gland. GH directly affects the body by activating the growth hormone receptor (GHR) on target tissues and indirectly by stimulating hepatocytes production of insulin growth factor-1 (IGF-1). In addition to their various roles in regulating growth and metabolism throughout the body, GH and IGF-1 have been shown to affect the brain at several specific sites. This includes, but is not limited to, the hypothalamus, hippocampus, and amygdala [20]. GH's ability to cross the blood-brain-barrier and evoke responses in various neural networks and brain regions provide evidence of its potential as a promising adjunctive pharmacotherapy post-stroke.

Furthermore, there is evidence that in addition to the systemic GH/IGF-1 axis, there may be a secondary neural GH/IGF-1 axis mitigating many of the GH effects. Following brain injury, the activation of GH receptors within the brain and the subsequent induction of IGF-1 may contribute to effects on neuronal survival, neurogenesis, synaptic plasticity, and cognitive function [21,22]. Importantly, GH administration can increase IGF-1 within the brain, suggesting that some of the neurological effects attributed to GH may be mediated by downstream IGF-1 signaling. GH appears to have both intrinsic effects within the brain as well as IGF-1 dependent effects, indicating that there are multiple complementary pathways at play in improving neural recovery.

When rhGH became available for replacement therapy in the early 1990s, clinicians who treated adults with hypopituitarism found that GH-deficient patients had significant cognitive impairments (attention, memory, processing speed) that improved with replacement [23]. The investigation of rhGH as a post-stroke potential therapy was driven by the discovery of an endogenous neural GH axis activated by a brain injury and the identification of GH as a possible neurotrophin [24]. The foundational work of Scheepens et al. first demonstrated that a neural GH axis is endogenously activated following a brain injury. Using moderate and severe hypoxic-ischemic injury models in juvenile rats, the authors identified intense GH-like immunoreactivity within regions of cellular loss as early as 3 days post-injury. This immunoreactivity was localized to neurons, myelinated axons, glial cells, and choroid plexus/ependymal cells within the injured hemisphere. These findings suggested that GH may circulate through the cerebrospinal fluid and exert neurotrophic effects directed toward injured neuronal and glial populations [25]. Beyond this, there has been increasing clinical evidence of GH deficiency as a frequent endocrinologic sequela following a brain injury, including a traumatic brain injury, a subarachnoid hemorrhage, and an ischemic stroke [26–28]. These findings, as demonstrated in Figure 1, lay the foundation for further preclinical and clinical investigations in the role of rhGH administration post-stroke for better functional and neurologic improvements.

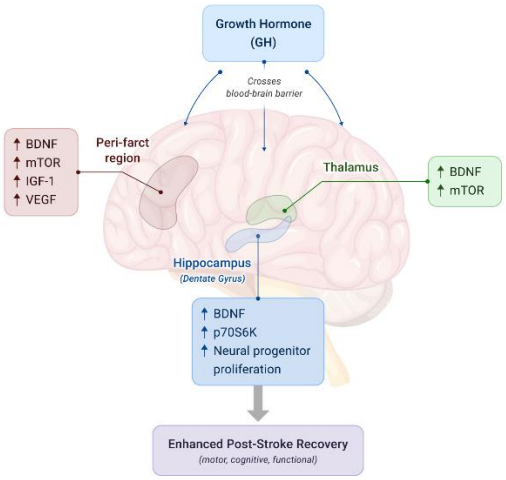


Figure 1. Growth Hormone's generalized effect on the brain.

3. Preclinical trials

Preclinical evidence for neurologic benefits in animal studies is encouraging and spans multiple complementary mechanisms including, but not limited to, neurotrophic factor regulation, synaptic plasticity, cerebrovascular remodeling, neurogenesis, and anti-inflammatory effects. Pathipati et al. investigated a delayed treatment protocol using chronic intracerebral rhGH infusion beginning 4 days after an endothelin-1-induced stroke in adult rats, continuing for 6 weeks with a recovery period of the same duration. Treatment groups demonstrated accelerated recovery of motor function ($p < 0.001$) and improved spatial memory on the Morris water maze ($p < 0.05$) at the study endpoint, with no effect on learning [29].

More recently, in 2018, Ong et al. demonstrated significant improvement in associative memory, reduced neural tissue loss, and significantly higher levels of neurotrophic factors (IGF-1, VEGF), presynaptic markers (synapsin-1), and myelination markers (myelin basic protein) in both the circulation and peri-infarct regions of young adult mice. Of note, rhGH treatment also increased the density and area coverage of major vascular markers (CD31, collagen IV) within the peri-infarct region, suggesting enhanced cerebrovascular remodeling and angiogenesis [30]. Building on this work, Sanchez-Bezanilla et al. (2022) employed the same photothrombotic stroke model and rhGH treatment regimen, in which rhGH was administered post-stroke to examine downstream molecular signaling mechanisms [31]. rhGH administration significantly elevated pro-BDNF expression in the peri-infarct region, hippocampus, and thalamus ($p < 0.01$). Additionally, rhGH increased the total mTOR expression in the peri-infarct region and thalamus ($p < 0.05$), as well as the total p70S6K levels in the hippocampus ($p < 0.05$). Because the thalamus is particularly susceptible to secondary neurodegeneration following a cortical stroke, the observed upregulation of pro-BDNF and mTOR in this region suggested that rhGH may influence pathways associated with secondary neurodegeneration through region-specific neuroplasticity signaling mechanisms.

In a related study, Sanchez-Bezanilla et al. (2020) reported that rhGH treatment produced substantial improvements in the motor performance, with recovery increasing by 50%–60% on cylinder and grid-walk assessments following a photothrombotic stroke affecting the motor and

sensory cortices. These behavioral improvements were accompanied by reduced tissue loss, increased proliferation of cells expressing neuronal markers (BrdU + /NeuN + cells), increased expression of synaptic plasticity markers, and greater angiogenesis within the peri-infarct region [15].

Beyond sole exogenous rhGH treatment improving anatomical and physiological brain structures post stroke, there is further evidence showing that the brain itself already utilizes this pathway to produce GH after injury to induce recovery. In two studies conducted by Dr. Devesa, it was found that after inducing a neural injury, the neural progenitor cells of the dentate gyrus in the Hippocampus endogenously upregulated GH production. This, in turn, contributed to their own further proliferation and recovery. Moreover, when exogenous GH was administered, it augmented the proliferative response, further hastening and improving the recovery [22,32]. The findings of these works, as summarized in Table 1, collectively show the microscopic and histologic changes in brain tissue seen with GH administration, and how they correspond with improved functional outcomes.

Table 1. Preclinical evidence for growth-hormone mediated post-stroke neuro-recovery.

Year	Author(s)	Methods	Primary Outcomes	Key Mechanisms (markers, anatomy) and Points
2001	Scheepens A, Sirimanne ES, Breier BH, et al. [25]	- Unilateral hypoxic-ischemic injury in juvenile rats (moderate: 15 min; severe: 60 min hypoxia) - 20 μg rat rhGH via ICV infusion starting 2 h post-injury; sacrificed at 3 days	Histological neuroprotection (no behavioral testing). Neuronal loss quantified by acid fuchsin/thionin staining and scored on 0–3 damage scale across 7 brain regions. rhGH reduced neuronal loss in frontoparietal cortex ($p < 0.001$), hippocampus ($p < 0.01$), dorsolateral thalamus ($p < 0.01$). No effect in striatum. rhGH-like immunoreactivity mapped via immunohistochemistry.	↑ rhGH-like immunoreactivity on injured neurons, myelinated axons, glia, choroid plexus, ependymal cells. Neuroprotection pattern correlated with constitutive neural GH receptor distribution, not IGF-I pattern. rhGH transported via CSF to injury sites.
2009	Pathipati P, Surus A, Williams CE, et al. [29]	- Unilateral endothelin-1 (ET-1)-induced focal stroke - Rat rhGH via ICV minipump starting 4 days post-stroke for 6 weeks; 6-week recovery period	Cognitive: Morris water maze -- probe trial (spatial memory, $p < 0.05$ improved); acquisition phase (learning, NS). Motor: Bilateral asymmetry test ($p < 0.001$ accelerated recovery on 1 of 3 tests); staircase reaching test; cylinder test. Histological: Infarct volume (cresyl violet). Systemic: Body weight (↑, $p < 0.01$); circulating IGF-1 (↓ halved, $p < 0.001$).	rhGH localized to ipsilateral SVZ, white matter tract, lesion, and penumbral regions. Improved spatial memory but not learning. Circulating IGF-1 halved, suggesting direct CNS-mediated cognitive effects.
2018	Ong LK, Chow WZ, TeBay C, et al. [30]	- Photothrombotic cortical stroke in young adult mice - rhGH (0.04 mg/day) SC via osmotic minipump starting 48 h post-stroke for 28 days	Cognitive: Touchscreen-based paired-associate learning (PAL) task (associative memory, P significant improvement); visual discrimination task. Histological: Neural tissue loss (cresyl violet). Molecular/IHC: Circulating and peri-infarct IGF-1 (ELISA); VEGF (ELISA); SYN-1, MBP (Western blot/IHC); CD31, collagen-IV (IHC with density and area coverage quantification).	↑ Associative memory (PAL). ↓ Neural tissue loss. ↑ IGF-1, VEGF (circulation + peri-infarct). ↑ SYN-1 (presynaptic), MBP (myelination). ↑ CD31, collagen-IV (angiogenesis) in peri-infarct.
2020	Sanchez-Bezanilla S, Åberg ND, Crock P, et al. [15]	- Photothrombotic stroke in adult male mice (motor/sensory cortex) - rhGH (0.04 mg/day) via osmotic minipump starting 48 h post-stroke for 28 days; BrdU injected 3 days post-treatment	Motor: Cylinder test (forelimb asymmetry, ~50%–60% improvement); grid walk test (foot faults/skilled locomotion, ~50%–60% improvement). Histological: Brain tissue loss (cresyl violet). Molecular/IHC: BrdU + cells (cell proliferation); DCX + cells (neurogenesis); SYN-1, PSD-95 (Western blot, synaptic plasticity); CD31, collagen-IV (IHC, angiogenesis) all quantified in peri-infarct region.	↑ Motor function 50-60%. ↓ Brain tissue loss. ↑ BrdU + (proliferation), DCX + (neurogenesis). ↑ SYN-1 (presynaptic), PSD-95 (postsynaptic). ↑ CD31, collagen-IV (angiogenesis) in peri-infarct.

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Year	Author(s)	Methods	Primary Outcomes	Key Mechanisms (markers, anatomy) and Points
2022	Sanchez-Bezanilla S, Beard DJ, Hood RJ, et al. [31]	- Photothrombotic cortical stroke in adult male mice - rhGH (0.04 mg/day, 0.25 μL/hr) via osmotic minipump starting 48 h post-stroke for 28 days; tissue at 30 days	Mechanistic study (no independent behavioral testing; same cohort as prior studies). Molecular: Western blot quantification of pro-BDNF, total-mTOR, phospho-mTOR, total-p70S6K, phospho-p70S6K across three brain regions (peri-infarct, hippocampus, thalamus). Pro-BDNF ↑ in all three regions ($p < 0.01$). Total-mTOR ↑ in peri-infarct and thalamus ($p < 0.05$). Total-p70S6K ↑ in hippocampus ($p < 0.05$). No significant changes in phosphorylated forms.	↑ pro-BDNF (peri-infarct, hippocampus, thalamus). ↑ Total-mTOR (peri-infarct, thalamus). ↑ Total-p70S6K (hippocampus). Region-specific molecular mechanisms identified.
2014	Devesa P, Agasse F, Xapelli S, et al. [22]	-Induced neural injury using Kainic Acid (KA) -Neural precursor cells were isolated from the hippocampus; cultures were treated with rhGH (500 ng/mL) for 24 h, and proliferation was assessed by BrdU incorporation	Mechanistic study (no independent behavioral testing). BrdU incorporation to quantify proliferation and TUNEL staining to assess apoptosis/survival in hippocampal SGZ-derived neural precursor cells. rhGH treatment ↑ BrdU + proliferating cells and ↓ apoptotic cells following growth-factor withdrawal. GHR blockade with pegvisomant ↓ proliferation and survival.	↑ Neural precursor proliferation (BrdU + cells). ↑ Cell survival/↓ apoptosis
2011	Devesa P, Reimunde P, Gallego R, et al. [32]	-Induced neural injury with KA -GH treatment (0.15 mg/kg) subcutaneously once every 24 hours for 4 days starting 12 hours or 10 days after insult	Mechanistic study (no independent behavioral testing) BrdU incorporation to quantify proliferation in the dentate gyrus; immunohistochemistry/in situ hybridization to assess hippocampal GH expression. KA injury ↑ BrdU + proliferating cells and ↑ endogenous hippocampal GH expression. Early exogenous GH treatment further ↑ progenitor proliferation, delayed GH treatment did not significantly ($p > 0.05$) enhance proliferation.	↑ Neural progenitor proliferation (BrdU + cells) in dentate gyrus following injury. ↑ Endogenous hippocampal GH expression after injury. Exogenous GH further ↑ proliferative response showing cooperation.

4. Preclinical trials

Clinical evidence for the neurologic benefit in human studies using rhGH for post-stroke rehabilitation has shown early evidence of benefit. Four major studies have demonstrated improvement in motor and/or cognitive function in patients administered with rhGH post-stroke. It is important to note that while these studies have not utilized or found a consistent rhGH dosage and are limited in sample size, they lay the groundwork to demonstrate the clinical efficacy in human populations and validate the need for further large-scale studies to be conducted.

In one of the first human trials that utilized rhGH for stroke patients in 2008, 14 patients who had documented completed strokes undergoing intensive rehabilitation were randomly assigned to either a control or rhGH treatment group [17]. Both groups received the same standard of care rehabilitation throughout the duration of the trial. Functional outcomes were measured using the Korean-Modified Barthel Index (K-MBI), Manual Muscle Strength (MMT), Fugl-Meyer assessment of the upper extremity (FMA), and Korean version of the Mini-Mental Status Examination (K-MMSE). The K-MBI is a validated index that measures functional independence in activities of daily living, with higher scores indicating greater independence [33]. After six months, both groups showed increases in their K-MBI score, but the rhGH-treated group showed statistically significant increases compared to the control ($p < 0.05$). Both the FMA and MMT, which measure muscle strength and functionality, demonstrated similar increases in both the control and treatment groups at the study endpoint, but with no statistical significance. Similar findings were observed with the K-MMSE, which evaluated global cognitive function [34]. Of note, the treatment group reported significantly less tiredness throughout the study time period ($p = 0.00$) compared to the control group. This is important because, as previously mentioned, post-stroke patients often face increased fatigue that can hinder their adherence to demanding physical rehabilitation. Both the K-MBI and fatigue findings evidenced the possible utility of rhGH treatment, in conjunction with standard rehabilitation, for better post-stroke patient outcomes.

Following Song's trial, in 2013, a similar human trial was initiated by Jin and Lee [35]. Here, 30 acute stroke patients between 2013–2016 were randomly assigned to three groups: rhGH for six months plus citicoline for six weeks (GH6), rhGH for 3 months plus citicoline 6 weeks (GH3), and the control group receiving only citicoline. Citicoline is a proposed neuroprotective nucleotide that has demonstrated positive neurologic outcomes in prior studies; this study aimed to evaluate if administration of rhGH could help beyond the baseline treatment with citicoline. Primary outcomes were the K-MBI and the modified Rankin Scale (mRS), which also evaluates the patient's degree of disability with activities of daily living, but higher scores indicate worsening disability. The GH6 group showed statistically significant increases on the K-MBI and decreases on the mRS when compared to the control group; GH3 did not show significant changes compared to the control. As before, this trial repeated findings that administering recombinant growth hormone, in conjunction with another stroke rehabilitation treatment, demonstrated improved outcomes as compared to the rehabilitation treatment alone. Furthermore, the above two studies used the same primary outcome in K-MBI scores, further validating the positive results of rhGH treatment on the post-stroke functionality improvement.

The largest human clinical trial was conducted in 2020 by Feng et al.: 60 original patients with diagnosed cognitive impairments due to stroke were randomized 1:1 to receive either rhGH subcutaneously or placebo injection for 6 months, and 43 patients completed the study [36]. All participants received the same rehabilitation therapy program throughout the study period. Primary outcomes included the following: Montreal Cognitive Assessment, serum neurotrophic factors,

biomarkers of glucose and lipid metabolism, and functional magnetic resonance imaging. The rhGH treatment groups had significantly lower triglycerides and LDL cholesterol, as well as increased IGF-1 levels ($p < 0.001$). Additionally, the treatment group demonstrated significantly higher Montreal Cognitive Assessment scores ($p < 0.001$) than the controls, demonstrating notable cognitive improvements. Lastly, the treatment group showed substantial increases in activation of brain regions associated with executive functioning, cognition, and memory, including the frontal lobe, putamen, temporal lobe, and thalamus ($p < 0.05$). All of these findings further support the notion that rhGH treatment has a major impact on global cognitive functioning post-stroke.

Most recently, the COURAGE trial, a multi-centric, randomized, open-label, controlled phase I-II clinical trial, evaluated the safety and functional effects of stimulating endogenous GH-related pathways after stroke using the epidermal growth factor (EGF) combined with the growth hormone secretagogue, Growth Hormone Releasing Peptide 6 (GHRP-6) [37]. Neurological and functional outcomes were measured via the National Institutes of Health Stroke Scale (NIHSS), Barthel Index, and mRS. The NIHSS evaluates stroke-related neurological deficits, with increasing scores representing increasing deficits. The patients were randomly assigned to three groups: standard of care plus EGF 75 μg + GHRP6 3.5 mg (Group I), EGF 75 μg + GHRP6 5 mg (Group II), or control with standard care for stroke (Group III). Group I had the largest decrease in NIHSS after six months as compared to Group III ($p = 0.031$). Both treatment groups (I and II) showed significant improvements in functionality, demonstrated by improved scores on both the mRS and Barthel index compared to Group III at 90 and 180 days ($p < 0.05$). As summarized in Table 2, this study's findings are consistent with that of others in the literature regarding functionality improvements post-stroke, particularly as an adjunctive neuroendocrine therapy in the post-stroke rehabilitation phase.

Table 2. Clinical evidence for growth-hormone mediated post-stroke neurorecovery.

Year	Author(s)	Methods	Primary Outcomes	Key Mechanisms (markers, anatomy) and Points
2012	Song J, Park K, Lee H, et al. [17]	- Pilot trial, non-randomized controlled - 37 patients with completed stroke (ischemic or hemorrhagic); rhGH group (n = 18) vs. control (n = 19); mean age ~58 years - rhGH 0.33 mg/day SC for 6 months, added to standard rehabilitation	Motor: Motricity Index (MI) - upper and lower extremity. Functional: Functional Ambulation Category (FAC); Korean Modified Barthel Index (K-MBI). Neurological: National Institutes of Health Stroke Scale (NIHSS). Body composition: Lean body mass, fat mass (DEXA). Biochemical: Serum IGF-1. rhGH group showed significantly greater improvement in K-MBI ($p < 0.05$) and FAC ($p < 0.05$) at 6 months. NIHSS improved in both groups. ↑ Lean body mass, ↓ fat mass in rhGH group. ↑ Serum IGF-1 ($p < 0.01$).	rhGH improved functional independence (K-MBI) and ambulatory function (FAC) beyond standard rehabilitation alone. Favorable body composition changes (↑ lean mass, ↓ fat mass) may contribute to motor recovery. ↑ IGF-1 correlated with functional gains. First clinical pilot demonstrating feasibility and benefit of rhGH add-on therapy in completed stroke.
2018	Jin GH, Lee JB [35]	-34 acute stroke patients (ischemic); rhGH group (n = 17) vs. control (n = 17); admitted within 7 days of stroke onset	Functional: Korean Modified Barthel Index (K-MBI). Neurological: NIHSS. Motor: Manual Muscle Test (MMT). Cognitive: Korean Mini-Mental State Examination (K-MMSE). Assessed at baseline, 1 month, and 3 months. rhGH group showed significantly greater improvement in K-MBI ($p < 0.05$) and K-MMSE ($p < 0.05$) at 3 months compared to controls. NIHSS and MMT improved in both groups without significant between-group differences.	rhGH add-on therapy in the acute phase improved functional independence (K-MBI) and cognitive function(K-MMSE) at 3 months. Demonstrated feasibility of early (acute phase) rhGH initiation. Lower dose (0.1 mg/day) than Song et al. still produced measurable benefits. First study to show cognitive improvement (K-MMSE) with rhGH in acute stroke.
2020	Feng X, Li G, Wu W, et al. [36]	- Retrospective controlled study - 60 patients with first-ever stroke (≥3 months prior) and diagnosed cognitive impairment; rhGH (n = 30) vs. placebo (n = 30); 43 completed (82.7%) - rhGH SC for 6 months + standard rehabilitative therapy	Cognitive: Montreal Cognitive Assessment (MoCA) - primary endpoint; improved from 16.31 (5.32) to 21.19 (6.54) ($p < 0.001$). Neuroimaging: Resting-state fMRI - amplitude of low-frequency fluctuations (ALFF) of BOLD signal; functional connectivity (FC) of default mode network (DMN). ↑ ALFF in frontal lobe, putamen, temporal lobe, thalamus ($p < 0.05$). Biochemical: Serum IGF-1 (↑ 32.6%, $p < 0.001$); triglycerides and LDL-cholesterol (↓); glucose and HbA1c (NS). Correlation: ΔALFF and ΔFC of DMN positively correlated with ΔMoCA and ΔIGF-1. No adverse effects.	First RCT with neuroimaging biomarkers demonstrating rhGH improves global and domain cognitive function in post-stroke cognitive impairment. MoCA improvement of ~5 points (clinically meaningful). fMRI showed increased neural activation in cognitively relevant regions (frontal, temporal, putamen, thalamus). DMN functional connectivity correlated with cognitive gains and IGF-1 elevation, providing a neurobiological mechanism linking GH to cognitive recovery. Favorable metabolic effects (↓ TG, ↓ LDL-C).

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Year	Author(s)	Methods	Primary Outcomes	Key Mechanisms (markers, anatomy) and Points
2024	Hernández-Bernal F, Estenoz-García D, Gutiérrez-Ronquillo JH, et al. [37]	Phase I/II multi-centric, randomized, open-label, controlled trial. - 36 acute ischemic stroke patients (CT-confirmed, 12 h from onset) - Group I: EGF + GHRP6 low dose (n = 10); 75 µg rEGF + 3.5 mg GHRP6 IV BID × 7 days - Group II: EGF + GHRP6 high dose (n = 10); 75 µg rEGF + 5 mg GHRP6 IV BID × 7 days - Group III: standard care control (n = 16); mean age 66 ± 11 years; 58.3% male; standard care only	Primary: Safety - SAEs over 6 months. SAEs: Control 56.2% vs. Group I 30% (OR 0.33) vs. Group II 20% (OR 0.19); only 2 events in 1 patient attributed to treatment. Secondary - Neurological: NIHSS at 90 and 180 days - favorable evolution in treated groups with moderate-to-strong effect size. Secondary - Functional: Barthel Index and modified Rankin Scale (mRS) at 90 and 180 days - favorable in treated groups. Utility-weighted mRS also showed benefit. Survival: Higher survival rate at 6 months in treated groups. Ancillary analysis with merged treated groups confirmed benefit.	First-in-human trial of EGF + GHRP6 combination for acute ischemic stroke. GHRP6 (growth hormone-releasing hexapeptide) stimulates endogenous GH/IGF-1 axis rather than providing exogenous GH directly. Demonstrated safety (primary endpoint met). Favorable neurological (NIHSS) and functional (Barthel, mRS) outcomes with moderate-to-strong effect sizes. Higher survival in treated groups. Ultra-early treatment window (12 h from onset) with 7-day IV course. Results supported advancement to Phase III. Represents a distinct pharmacological approach (GH-axis stimulation) vs. direct rhGH replacement.

5. Safety

As with most new therapeutics, safety has been a major consideration throughout these original clinical trials. Both Song et al.'s and the COURAGE trial evaluated safety as a major endpoint. In Song et al.'s trial, there were no adverse effects documented during the study and within the following three years in the treatment group. The patients' complete blood count (CBC), blood urea nitrogen (BUN), creatinine, glucose, and electrolytes were continuously followed, with no significant changes to the normal range [17]. It is important to note that this trial excluded patients with impaired glucose tolerance, hypertension, and known serum tumor markers due to the possibility of rhGH negative interaction. While this is reasonable in the preliminary determination of rhGH administration, given the known systemic effects of GH on increased insulin resistance and fluid retention, Feng's study was able to demonstrate no significant changes to hemoglobin A1c, glucose, or fluid status. This helps support the overall potential utility of GH in a variety of patients, including patients with diabetes and hypertension, as they are known stroke comorbidities. Lastly, in the COURAGE trial, it was found that less than 30% of serious adverse effects had a causal relationship to the treatment. Furthermore, "At the end of the study, the ethical committees and the independent data monitoring committee issued a favorable assessment in terms of the safety of the therapeutic combination under investigation, endorsing the continuity of the clinical development of the project." [37]. Both studies underline the potential safety of rhGH therapy and validate continued research to better understand its possible utilization as a therapeutic tool.

6. Conclusions

rhGH treatment has demonstrated encouraging clinical potential in improving patient functionality and outcomes post-stroke. Numerous pre-clinical studies have demonstrated its ability to increase neurotrophic factors, improve neuroregeneration, and enhance circulation in peri-infarct regions. Human clinical trials have consistently established rhGH treatment ability to improve the patient scores on a variety of clinical indices, ranging from the improvement of activities of daily living to decreasing neurologic deficits. This is especially evident when rhGH is combined with standard-of-care physical rehabilitation therapies and/or with known neuroregenerative pharmaceuticals. These findings support the notion that rhGH can be used in conjunction with current therapies to potentiate enhanced outcomes rather than as a replacement or alternative. Furthermore, clinical trials have not identified large safety concerns or demonstrated largely positive safety profiles, but the small cumulative sample size is inadequate to establish complete safety.

Given the mechanistic rationale and encouraging early results, further research must be conducted to address several gaps that remain before rhGH therapy can be considered an adjunct to standard of care in post-stroke rehabilitation. Feng et al.'s single-center randomized controlled trial and Leonhardt et al.'s phase II pilot studies were both relatively small. Additionally, the optimal dosing, timing of initiation, treatment duration, and broader applications remain unanswered. Larger, multicenter randomized controlled trials with standardized endpoints are needed to define the target population, to establish greater efficacy, and to elucidate treatment protocols. Despite the need for further research, rhGH has demonstrated a promising future for those post-strokes to see better outcomes and improved lives.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

Emmanuelle Zakheim: conceptualization, investigation, writing- original draft, writing-review and editing; Daniel Moon: investigation, writing-original draft, writing-review and editing; Wesley Tran: investigation, writing-review and editing; Ephrem Gerald: investigation, writing-reviewing and editing; Mohamed Ahmed: conceptualization, supervision, writing-reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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