Role of GLP-1 receptor agonists in sepsis and their therapeutic potential in sepsis-induced muscle atrophy (Review)

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Abstract. Sepsis-induced myopathy (SIM) is a common complication in intensive care units, which is often associated with adverse outcomes, primarily manifested as skeletal muscle weakness and atrophy. Currently, the management of SIM focuses on prevention strategies, as effective therapeutic options remain elusive. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) have garnered attention as hypoglycemic and weight-loss agents, with an increasing body of research focusing on the extrapancreatic effects of GLP-1. In preclinical settings, GLP-1RAs exert protective effects against sepsis-related multiple organ dysfunction through anti-inflammatory and antioxidant mechanisms. Based on the existing research, we hypothesized that GLP-1RAs may serve potential protective roles in the repair and regeneration of skeletal muscle affected by sepsis. The present review aimed to explore the relationship between GLP-1RAs and sepsis, as well as their impact on muscle atrophy-related myopathy. Furthermore, the potential mechanisms and therapeutic benefits of GLP-1RAs are discussed in the context of muscle atrophy induced by sepsis.

Contents

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1. Introduction

The latest definition of sepsis comes from a consensus reached by the international medical community in 2016, specifically the 'Sepsis-3' definition, which characterizes sepsis as 'a life-threatening organ dysfunction caused by a dysregulated host response to infection' (1). Sepsis is a leading cause of mortality in the intensive care unit (ICU) and poses a threat to human health (2-4). Over decades of development in critical care medicine, effective early identification and therapeutic interventions, including early infection control, maintenance of hemodynamic stability and modulation of the host response, have successfully reduced mortality rates during the acute phase of sepsis, leading to an increase in the number of sepsis survivors (5-7). However, among survivors, the risk of developing persistent acquired weakness syndromes is markedly increased (8). Therefore, the long-term prognosis of sepsis remains unsatisfactory. The muscle weakness induced by sepsis is a common complication that often leads to a state of chronic critical illness (9). This condition is characterized by a decline in muscle strength, clinically referred to as ICU-acquired weakness (ICU-AW), which includes sepsis-induced myopathy (SIM) (8-10). The atrophy of limb skeletal muscles can lead to decreased limb strength, and if respiratory muscles are affected, it may result in respiratory weakness, increasing the risk of severe complications such as pulmonary infections and respiratory failure in critically ill patients (10). A meta-analysis on sarcopenia and the risk of mortality in patients with sepsis indicated that, compared with patients without sarcopenia, those with sarcopenia have higher early mortality risks (during hospitalization or within 1 month of illness), as well as increased mortality risks at 3-6 months after sepsis (11). This highlights the profound impact of ICU-AW on the long-term recovery of

patients with sepsis, as well as its contribution to prolonged hospital stays.

SIM refers to clinically diagnosed weakness in critically ill patients that cannot be attributed to non-critical illness causes, with an incidence rate as high as 40% among critically ill patients in the ICU (8,12). SIM is characterized by its systemic and symmetrical nature, presenting with weakness in the limbs (more proximal than distal) and respiratory muscles, while facial and ocular muscles are generally unaffected (13-15). William Osler first described sepsis-associated muscle atrophy in 1892 as 'the rapid wasting of flesh'. However, due to the limitations of medical knowledge at the time, the primary focus was on patient survival rather than long-term complications (16). With the rapid advancements in critical care medicine at present, there is a clearer understanding of the risk factors, pathophysiology, diagnosis and treatment strategies for SIM. Nevertheless, effective therapeutic options for SIM remain unavailable, with prevention remaining paramount (8-10). The importance of early avoidance or treatment of sepsis, anti-inflammatory strategies, nutritional support and subsequent rehabilitation is emphasized in previous studies. Nutritional support and rehabilitation training are often considered to be supportive interventions rather than therapeutic measures. The main purpose of nutritional support is to alleviate malnutrition and promote muscle protein synthesis, while the purpose of rehabilitation training is to maintain muscle function and prevent further atrophy. However, developing precise and effective treatments remains a challenge (13,17).

Glucagon-like peptide-1 (GLP-1) is a peptide hormone comprising 30 or 31 amino acids, and is secreted by L cells in the distal gut, α-cells in the pancreas, and the hypothalamus and nucleus of the solitary tract in the central nervous system (18). Endogenous GLP-1 exists in two forms: A proglucagon corresponding to the amidation of C-terminal Arg, GLP-1(7-36) amide, consisting of 30 amino acids, which is the main form of GLP-1 in the human body and has a high biological activity. The other is longer and unaminated, GLP-1(7-37), which consists of 31 amino acids (18). GLP-1 effectively reduces glycosylated hemoglobin A1c and fasting plasma glucose levels, while also promoting weight loss and decreasing systolic blood pressure, with a low incidence of hypoglycemia (18). Therefore, GLP-1 receptor (GLP-1R) agonists (GLP-1RAs) are recommended as early and ongoing treatment options for patients with type 2 diabetes mellitus (T2DM) in the clinical practice guidelines provided by the American Association of Clinical Endocrinologists and the American Diabetes Association/European Association for the Study of Diabetes (19,20). GLP-1RAs reduce weight through various mechanisms, including appetite suppression, reduced hunger and increased satiety, resulting in decreased energy intake (21). Therefore, GLP-1RAs are often utilized as weight-loss medications (21). Additionally, GLP-1 exerts various biological effects, including reducing neuroinflammation, promoting nerve growth, improving cardiac function, delaying gastric emptying, modulating lipid metabolism and reducing fat deposition (22). As a result, GLP-1 has promising applications in the treatment of various diseases, such as sepsis and muscular atrophy (19-22). Research indicates that GLP-1R represents a novel therapeutic target for sepsis, capable of modulating the immune response and the release of inflammatory factors in critically ill patients, particularly those with sepsis, thereby providing organ protection (23). One study has also indicated that GLP-1RAs can be utilized in the treatment of skeletal muscle atrophy in diabetic patients with chronic liver disease (CLD) (24). These findings suggest that GLP-1RAs may have substantial potential in the treatment of SIM, prompting a review of the physiological functions of GLP-1 and its therapeutic potential in sepsis and SIM.

2. Physiological functions of GLP-1

GLP-1 is a 30- or 31-amino acid peptide hormone, derived from the proglucagon gene, and expressed by specific intestinal endocrine L cells, pancreatic α-cells and a subset of neurons within the nucleus of the solitary tract (NTS) (18). This peptide exists in two active forms, GLP-1(7-36) amide and GLP-1(7-37), both of which are functionally equivalent, although the former is more abundant (25-28). Due to enzymatic degradation and renal clearance (29), endogenous GLP-1 has a short half-life of 1-2 min (30,31). The primary mechanisms involved in GLP-1 degradation are enzymatic cleavage and hepatic metabolism (30,31). Dipeptidyl peptidase-4 (DPP-4) is the main enzyme responsible for GLP-1 breakdown, and cleaves GLP-1 to produce inactive forms, including GLP-1(9-36) amide or GLP-1(9-37), reducing its biological activity (22,32,33). Most circulating GLP-1 is degraded upon entry into the DPP-4-enriched mucosal vasculature, leaving only 10-15% of GLP-1 to reach systemic circulation, where it undergoes hepatic metabolism (30,33,34). Renal clearance primarily eliminates inactive fragments or intact GLP-1 via glomerular filtration. Thus, patients with renal impairment may experience delayed elimination of GLP-1 metabolites; however, this does not substantially impact its biological effects (35).

GLP-1 is predominantly secreted by enteroendocrine L cells located in the distal ileum and colon, with food intake serving as a principal physiological stimulant. Plasma GLP-1 levels rise within minutes postprandially, even before nutrients reach L cells in the small intestine, indicating that GLP-1 secretion is primarily regulated by neural and endocrine stimuli (18). Plasma levels of GLP-1 are low in the fasting state, in the range of 5-10 pmol/l, and increase rapidly after eating, reaching 15-50 pmol/l (29). GLP-1 exerts its effects through GLP-1R, a member of the class B G protein-coupled receptor family, mainly by activating the cAMP-protein kinase A (PKA) pathway to promote insulin release and improve insulin resistance (30,36). GLP-1R is widely expressed across various tissues, including the pancreas, lungs, kidneys, central nervous system, heart, vascular smooth muscle, gastrointestinal tract and vagus nerve (22,25,33,37,38). One study has also identified the liver, skeletal muscle and adipose tissue as additional GLP-1 targets (39), further highlighting its diverse and significant biological functions.

GLP-1 possesses multiple biological functions and substantial pharmacological potential, including but not limited to lowering blood sugar and weight control (40-49) (Fig. 1). As an incretin hormone, it stimulates insulin synthesis and secretion in the pancreas via PKA and exchange protein directly activated by cAMP signaling

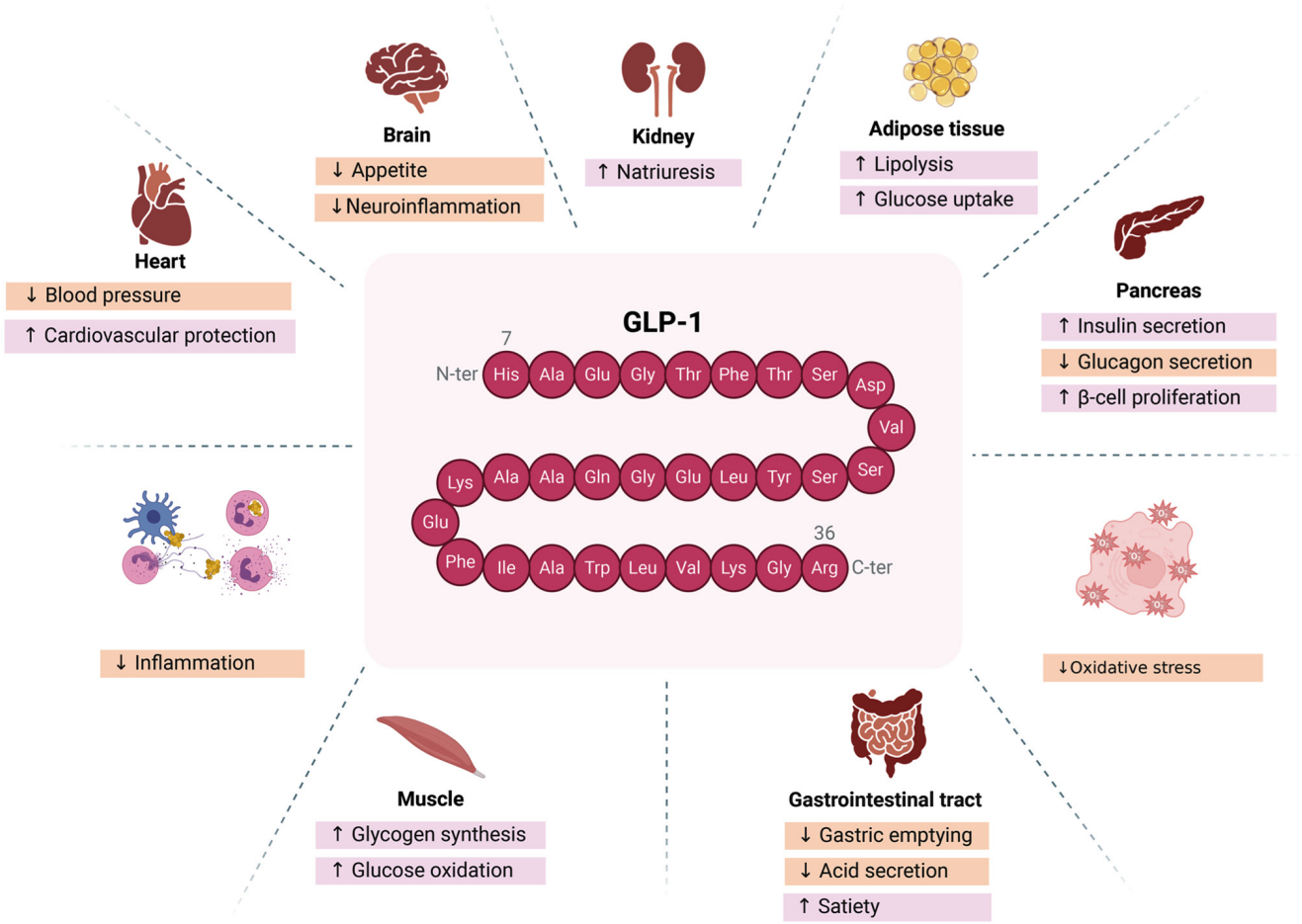

Figure 1. Physiological functions and therapeutic potential of GLP-1. GLP-1 is a 30-amino acid peptide hormone derived from proglucagon, primarily secreted by intestinal L cells in response to food intake. GLP-1 exerts its effects through GLP-1 receptors, which are widely distributed across various tissues. GLP-1 inhibits glucagon secretion, delays gastric emptying, decreases appetite and enhances satiety, serving a crucial role in anti-diabetic and anti-obesity treatments. Additionally, GLP-1 exhibits neuroprotective, anti-inflammatory and cardiovascular protective effects. GLP-1, glucagon-like peptide-1.

pathways, thereby enhancing glucose metabolism (40-42). In certain cases, it can also stimulate β-cell proliferation and inhibit β-cell apoptosis (43). GLP-1 reduces blood glucose by inhibiting glucagon secretion, an effect that is as significant as its insulinotropic action in lowering blood glucose levels, as demonstrated in a study on patients with T2DM (44). Additionally, GLP-1 suppresses food intake, contributing to weight reduction (21). Long-acting GLP-1RAs have been shown to influence body weight by modulating food intake and energy expenditure through various hypothalamic pathways (45). By acting on GLP-1R, GLP-1 also delays gastric emptying and enhances satiety by inhibiting postprandial gastrointestinal motility and gastric acid secretion, making GLP-1 analogues promising anti-obesity agents (33,46). Furthermore, GLP-1 has been reported to reduce water intake independently of its effect on food intake (47). Pharmacological evidence suggests that GLP-1 serves a key role in stress response regulation, with central GLP-1R signaling being critical in the acute response to stress and aversive stimuli (48,49). Additionally, GLP-1 enhances cognitive function, improves memory and exerts neuroprotective effects (50,51). In addition, GLP-1 promotes lipolysis and glucose uptake, reduces lipid deposition, and exhibits various functions, including anti-inflammatory effects, blood pressure regulation, cardiovascular protection and antioxidative stress properties (22,33).

GLP-1 analogues have been widely used to treat T2DM and obesity (52,53). Liraglutide and exendin-4 (Ex-4) are commonly prescribed GLP-1 analogues, which reduce cardiovascular-related mortality, non-fatal myocardial infarction and non-fatal stroke in hospitalized patients with T2DM (52). Liraglutide also reduces the incidence of diabetic nephropathy in T2DM (53). An animal study demonstrated that Exendin-4 treatment reduced infarct volume and improved functional deficits while inhibiting oxidative stress, the inflammatory response and cell death after reperfusion (54). Furthermore, GLP-1 analogues have been demonstrated to alter metabolic, bioenergetic and contractile characteristics within risk and non-risk myocardial regions following ischemic injury, exerting cardioprotective effects (55). Research has further demonstrated the protective role of GLP-1 in organs such as the gastrointestinal tract (56), lungs (57) and liver (58). A study has also reported that GLP-1RAs can treat diabetes-induced skeletal muscle atrophy by promoting glycogen synthesis and glucose oxidation (24). Additionally, GLP-1RA has emerged as a novel therapeutic target for sepsis, protecting organs by modulating immune responses and inflammatory cytokine release in patients with sepsis (23,59-64).

3. Pathophysiology of sepsis-associated muscle atrophy

Sarcopenia is a syndrome marked by a progressive reduction in skeletal muscle mass, quality and strength, often exacerbated by aging and reduced activity (65). Various systemic diseases, including cancer, renal failure, chronic obstructive pulmonary disease, sepsis and trauma, also accelerate sarcopenia progression (66). In sepsis, pathophysiological changes include sympathetic nervous system activation, and excessive release of catabolic hormones (catecholamines and glucocorticoids) and pro-inflammatory cytokines. This catabolic state leads to anabolic resistance, tipping the balance between protein synthesis and degradation towards net catabolism in critically ill patients (67,68). As muscle mass declines, muscle strength deteriorates, ultimately resulting in ICU-AW (67). The pathogenesis of SIM is complex and remains incompletely understood. This condition primarily arises from an imbalance between muscle protein synthesis and degradation, alongside reduced force-generating capacity, often secondary to neuropathy, myofibrillar disruption, sarcoplasmic reticulum (SR) impairment, altered excitability and mitochondrial dysfunction (68).

Increased proteolysis in skeletal muscle. Protein degradation in skeletal muscle cells primarily involves four proteolytic systems: The ubiquitin-proteasome system (UPS), calpains, caspases and the autophagy-lysosome pathway (13,68,69). The UPS serves a critical role in degrading most damaged proteins, which, after being ubiquitinated, are broken down in the 26S proteasome. Key E3 ubiquitin ligases in this system, muscle RING finger 1 (MuRF1) and muscle atrophy F-box (MAFbx/atrogin-1), are essential in skeletal muscle degradation (68,69). MuRF1 hydrolyzes myosin in thick filaments, while MAFbx/atrogin-1 likely suppresses protein synthesis by downregulating eukaryotic translation initiation factor 3 subunit F (eIF3f; an essential protein synthesis initiator) and MyoD (a crucial muscle differentiation transcription factor) (70-72). The NF-κB pathway and its inhibitors interact to regulate UPS activation (68,69). During sepsis, elevated inflammatory cytokine levels enhance ubiquitination and the degradation of NF-κB inhibitors (IkB), which in turn activates the UPS pathway (73). Excessive expression of TNF and NF-κB increases the levels of muscle-specific E3 ligases (MuRF1 and atrogin-1), ultimately leading to proteolysis in respiratory and limb muscles, manifesting as difficulties in ventilator weaning and muscle weakness in patients (73,74).

Calpain activation is associated with SIM (75,76). A study has indicated that calpain activation in septic muscle leads to increased protein degradation, while concurrently downregulating Akt activity, thereby reducing protein synthesis (68). The PI3K/Akt signaling pathway, which maintains protein balance, is inhibited under catabolic conditions such as sepsis, inflammation and immobilization, promoting UPS activation and protein degradation (68). Reduced Akt activity alleviates inhibition of FoxO, a transcription factor that upregulates the expression of the muscular atrophy factor (atrogin-1/MAFbx), and the upregulation of muscle atrophy factor accelerates muscle atrophy (68). Low PI3K activity induces BAX expression, which subsequently releases cytochrome c from mitochondria into the cytosol, thereby activating caspase-3 (68). Caspases, while widely recognized for their role in apoptosis, are now being implicated in sepsis-induced myopathies (68,77). Studies in infected animal models have demonstrated that caspases, by cleaving cytoskeletal proteins in the diaphragm, led to muscle weakness (68,77). Similarly, the autophagy-lysosome pathway, crucial for skeletal muscle degradation, becomes hyperactivated under catabolic, oxidative stress and pro-inflammatory conditions, which exacerbates muscle atrophy through excessive protein breakdown (78). Autophagy is regulated by multiple factors, including hypoxia, infection and stress (79,80). Hussain *et al* (79) demonstrated that prolonged mechanical ventilation led to disuse atrophy of the diaphragm, which further triggered the oxidative stress response and activated the FoxO1 transcription factor, thereby inducing skeletal muscle protein degradation through the autophagy lysosomal pathway (80).

Decreased protein synthesis. Protein synthesis is primarily regulated through two signaling pathways, the insulin/insulin-like growth factor 1 (IGF-1) and mTOR signaling pathways, both of which are essential for anabolic processes. The insulin/IGF-1-Akt pathway enhances protein synthesis by activating the mTOR pathway, while inhibiting FoxO (73,81). Specifically, the IGF-1-PI3K-Akt-mTOR cascade promotes protein synthesis and suppresses protein degradation by phosphorylating downstream FoxO, thereby inhibiting E3 ligases (MuRF1 and atrogin-1) (73,81). In addition to activating the IGF-1/Akt pathway for protein synthesis, IGF-1 also stimulates the MAPK cascade, promoting myoblast proliferation (68,69). However, during sepsis and muscle atrophy, IGF-1 levels in the muscle decline, which reduces protein synthesis (81-83). FoxO promotes the expression of atrophy-related genes (atrogenes), and under critical conditions such as sepsis, decreased IGF-1-PI3K-Akt-mTOR signaling increases FoxO-mediated expression of atrogenes, reducing protein synthesis (81-83). Nystrom *et al* (84) have confirmed this, showing that IGF-1 administration in septic mice enhanced muscle protein synthesis and alleviated sepsis-induced muscle atrophy.

The mTOR pathway, another critical regulator of protein synthesis, is activated by growth factors, nutrients, insulin and other signals, facilitating anabolic processes and regulating biosynthesis, including protein synthesis (69,85). Upon activation, mTOR phosphorylates downstream targets, including eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and S6K1, to promote protein translation (69,85). A study has shown that sepsis inhibited mTOR activity, and suppressed the phosphorylation of 4E-BP1 and S6K1 (86). Non-phosphorylated 4E-BP1 binds tightly to eukaryotic translation initiation factor 4E (eIF4E), a subunit of the eukaryotic initiation factor 4F complex responsible for mRNA cap binding, thereby inhibiting eIF4E-mediated initiation of protein synthesis (85). Similarly, dephosphorylation of S6K1, which activates the S6 protein of the 40S ribosomal subunit, inhibits translation (85). Sepsis-induced mTOR suppression may, in part, be attributed to excessive pro-inflammatory cytokines (87).

Mitochondrial dysfunction. Mitochondrial dysfunction is a key factor in the development of critical illness myopathy, especially in sepsis. Mitochondria are central to energy conversion,

biosynthesis and signaling, with ATP production being essential for muscle contraction. Mitochondria also regulate calcium homeostasis, reactive oxygen species (ROS) production, intracellular communication and apoptosis. Structural damage and dysfunction in mitochondria lead to ATP deficiency, ROS overproduction and cytochrome c release, potentially resulting in organ failure (88,89). Research indicates that the accumulation of damaged mitochondria contributes to motor neuron and muscle fiber degeneration (88,89). During sepsis, excessive ROS production exacerbates mitochondrial dysfunction, creating a feedback loop that worsens oxidative damage (13,90). Studies have indicated reduced expression and activity of respiratory chain complexes I, III and IV in muscle tissue of critically ill patients, partially explaining the muscle weakness observed in critically ill patients (13,90).

Calcium homeostasis dysregulation. Calcium level fluctuations affect protein degradation, since calpain activity and UPS activation are calcium-dependent (69). Additionally, calcium ions are crucial for muscle contraction, influencing myosin ATPase activity, glycolysis and oxidative metabolism (69). The SR serves a role in maintaining calcium homeostasis (91,92). Friedrich *et al* (91) demonstrated that serum from critically ill patients affected SR Ca^{2+} release in mammalian muscle fibers, altering membrane excitability and excitation-contraction coupling. Similarly, Zink *et al* (92) reported decreased SR Ca^{2+} release in skeletal muscle fibers during sepsis, suggesting that disrupted Ca^{2+} homeostasis may contribute to muscle dysfunction in sepsis.

Neuropathy and membrane excitability impairment. Sepsis induces microvascular changes in the endoneurium, increasing vascular permeability and allowing toxic factors to infiltrate nerve endings (13,93). Increased permeability leads to endoneurial edema, which can impair energy transmission along axons, ultimately resulting in axonal death (13,93). Under physiological conditions, cellular permeability to Na^+ and K^+ ions forms the basis for electrophysiological stability. In sepsis, alterations in Na^+ pump function can lead to dysregulated membrane excitability. Notably, inflammatory cytokines exert neurotoxic effects, causing persistent membrane depolarization, a phenomenon referred to as 'denervation' (13,69,93,94). Na^+ channel inactivation in ICU-AW may lead to rapid, reversible hypo- or non-excitability, impairing both neuronal and muscular function (13,69,93,94).

4. GLP-1RAs and septic multi-organ dysfunction

Research on the extrapancreatic effects of GLP-1RAs is a rapidly developing field. As GLP-1Rs are distributed in the pancreas, kidneys, lungs, heart, intestines and other organs, an increasing number of studies have focused on the protective effects of GLP-1RAs on organ function (22,23,63). Sepsis is a complex syndrome characterized by a systemic inflammatory response leading to severe multi-organ dysfunction (95). Numerous studies (23,59-64) have demonstrated that GLP-1RAs exert immunomodulatory and protective effects in sepsis-related organ dysfunction, including in the lungs, brain, heart, kidneys, liver, gastrointestinal tract and vasculature (Fig. 2).

GLP-1RAs and septic lung injury. Sepsis often affects the respiratory system, leading to acute respiratory distress syndrome (ARDS), the most common cause of which is sepsis (96). The pathogenesis of ARDS primarily involves excessive inflammation and damage to the alveolar-capillary barrier, resulting in the accumulation of inflammatory cells, increased levels of pro-inflammatory factors and injury to alveolar epithelial cells. The activation and recruitment of inflammatory cells, including macrophages and neutrophils in the pulmonary circulation, serve crucial roles in the development and progression of septic lung injury (97,98). Neutrophils activate Toll-like receptors and $CD14^+$ T cells, promoting the release of inflammatory mediators [IL-1β, TNF-α, nitric oxide (NO) and ROS] (97,98). Key pathophysiological changes in acute lung injury caused by sepsis include infiltration of inflammatory cells, release of inflammatory mediators, thrombus formation in pulmonary capillaries, interstitial pulmonary edema and pulmonary fibrosis, with clinical manifestations primarily being progressive dyspnea and persistent hypoxemia secondary to sepsis (99).

Baer *et al* (97) demonstrated that liraglutide, a GLP-1RA, could mitigate sepsis-induced acute lung injury by reducing various inflammatory markers in the lungs, including the number of immune cells and the concentration of pro-inflammatory factors. The anti-inflammatory effects of liraglutide may be mediated through the inhibition of the NLR family pyrin domain containing 3/IL-1β inflammasome and the stimulation of IL-10 (97). Animal experiments indicated that liraglutide could decrease the transcription of pro-inflammatory factors such as IL-1β at the 6-h time point in septic mice, while increasing IL-10 mRNA expression (97). The study also found that liraglutide not only promoted the resolution of sepsis-induced inflammation but also did not impair the ability of the host to clear bacteria (97). GLP-1RAs may reduce excessive inflammation and damage to the alveolar-capillary barrier, possibly by inhibiting its inflammatory response and subsequent immune cell recruitment, or through direct effects on alveolar macrophages and circulating immune cells, altering their migration, proliferation and phenotype/activation (97). The beneficial effects of GLP-1RAs on septic lung injury were similarly confirmed by Guo *et al* (60), who found that liraglutide treatment in mice with sepsis induced by bacterial pneumonia could reduce the bacterial load, improve animal survival rates, decrease lung inflammatory cells and cytokines, and enhance the production of pulmonary surfactant phospholipids and surfactant proteins A and B, thereby alleviating acute lung injury and mortality due to pneumonia-induced sepsis. Additionally, liraglutide can modulate pulmonary surfactant through autophagy inhibition to mitigate sepsis-induced acute lung injury (57).

GLP-1RAs and sepsis-associated encephalopathy (SAE). The central nervous system is one of the organs most susceptible to sepsis, with 50-70% of septic patients experiencing SAE. The pathogenesis of SAE primarily involves neuroinflammation, blood-brain barrier (BBB) damage, cerebral microcirculatory dysfunction and mitochondrial dysfunction (61,100,101). Clinical manifestations of SAE range from behavioral disturbances to altered consciousness, including delirium and

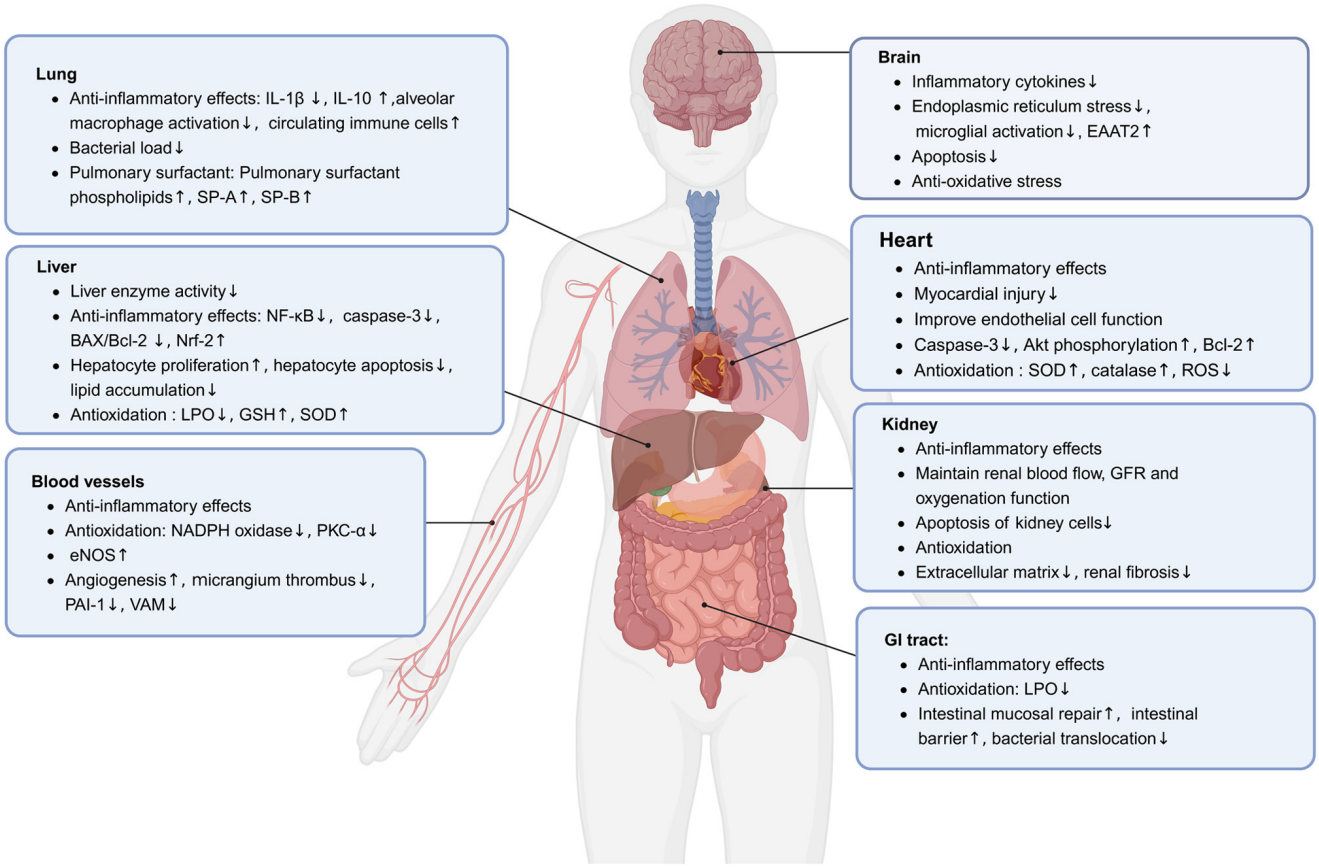

Figure 2. Protective mechanisms of GLP-1RAs in septic multi-organ dysfunction. Due to the widespread distribution of GLP-1 receptors in organs such as the pancreas, kidneys, lungs, heart and intestines, a growing number of studies have focused on the protective effects of GLP-1RAs on organ function during sepsis (23,59-64). In preclinical settings, GLP-1RAs possess potential immunomodulatory and protective effects in sepsis-related organ dysfunction, including in the lungs, brain, heart, kidneys, liver, GI tract and vasculature. EAAT2, excitatory amino acid transporter-2; eNOS, endothelial nitric oxide synthase; GFR, glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1RAs, GLP-1 receptor agonists; GSH, glutathione; LPO, lipid peroxidation; Nrf2, nuclear factor erythroid 2-related factor 2; PAI-1, plasminogen activator inhibitor type 1; PKC-α, protein kinase C-α; ROS, reactive oxygen species; SOD, superoxide dismutase; SP-A, surfactant protein A; SP-B, surfactant protein B; VAM, vascular adhesion molecules.

coma, complicating its management due to a lack of specific diagnostic criteria (61,100,101).

Endogenous GLP-1 can also be produced by neurons in the NTS of the brain stem, helping to regulate insulin resistance, food intake, neuroprotection, and learning and memory dysfunction (33). Neuroinflammation and excessive activation of microglia are neuropathological features of SAE (100,102). The breakdown of the BBB during sepsis facilitates the entry of inflammatory mediators and other substances from the periphery into the brain, leading to microglial activation and subsequent neuronal dysfunction (100,102). Research by Yi *et al* (61) in a mouse model of sepsis indicated that the GLP-1/GLP-1R pathway could regulate the progression of SAE. Activation of GLP-1/GLP-1RA may inhibit endoplasmic reticulum stress, microglial activation, production of inflammatory cytokines and hippocampal cell apoptosis, thereby improving survival rates and cognitive deficits in cecal ligation and puncture mice. The authors also demonstrated that liraglutide protected microglia through modulation of the cAMP/PKA/cAMP response element binding protein (CREB) signaling pathway (61). Fang *et al* (103) demonstrated that recombinant human GLP-1 improved neurological deficits and reduced infarct volume in rats with middle cerebral artery occlusion by inhibiting oxidative stress and apoptosis, and promoting excitatory amino acid transporter-2 expression.

GLP-1RAs and sepsis-associated myocardial injury. Sepsis-induced myocardial injury (SIMI) is one of the most common complications of sepsis and a leading cause of death. The pathogenic factors of SIMI include the release of myocardial depressant factors, upregulation of NO, impairment of myocardial calcium homeostasis and mitochondrial dysfunction (104,105). SIMI is primarily characterized by myocardial ischemia and hypoxia, impaired contractile function, and reduced left ventricular ejection fraction, leading to inadequate tissue and organ perfusion (104,105). Research suggests that the occurrence of SIMI may be related to the activation of Bax and caspase-3, and the inhibition of Bcl-2, which induces apoptosis of myocardial cells during sepsis. The apoptosis involved in SIMI encompasses the activation or inhibition of multiple pathways, including TNF-α and MAPK-related, PI3K/AKT/mTOR, and NF-κB signaling pathways, with the release of various inflammatory factors that directly lead to myocardial damage, resulting in increased secretion of inducible NO synthase and excessive production of NO (98,104). Excessive NO inhibits type I calcium channels and mitochondrial function in myocardial

cells, resulting in impaired contractile function and decreased cardiac output (98,104).

The cardioprotective effects of GLP-1RAs primarily include anti-inflammatory actions, reduction of myocardial ischemic injury, alteration of lipid synthesis and secretion, and improvement of endothelial dysfunction (106). A study has revealed that liraglutide increased cAMP formation in a GLP-1R-dependent manner *in vitro* and reduced the activation of caspase-3 in myocardial cells (107). GLP-1RAs engage pro-survival pathways in the mouse heart, improving outcomes following myocardial infarction and enhancing survival (107). Exenatide, a GLP-1 analog, has been shown by Timmers *et al* (108) to reduce myocardial infarction size, and prevent deterioration of both systolic and diastolic heart function. Following exenatide treatment, the levels of phosphorylated Akt and Bcl-2 were increased, while active caspase-3 expression was decreased. There was also a reduction in nuclear oxidative stress, and an increase in the activity of superoxide dismutase (SOD) and catalase, which could reduce infarct size in patients with acute myocardial infarction (108). Another study has also confirmed the beneficial effects of GLP-1 analogs in myocardial infarction (109). Compared with the placebo group, treatment with the GLP-1 analog liraglutide reduced the rates of non-fatal myocardial infarction, non-fatal stroke and hospitalization for heart failure (52). Additionally, Chang *et al* (110) demonstrated that exenatide exerted cardioprotective effects against oxidative stress-induced injury both *in vitro* and *in vivo*, which was potentially attributed to the clearance of oxidative stress products (such as ROS), increased concentrations of antioxidant defense enzymes and suppression of myocardial cell apoptosis. The authors also suggested that the anti-apoptotic effects of exenatide were at least partially related to the activation of the PI3K/Akt signaling pathway (110).

GLP-1RAs and sepsis-induced kidney injury. Acute kidney injury (AKI) occurs in 40-50% of patients with sepsis, increasing the in-hospital mortality risk by 6-8 times (111). The pathophysiology of sepsis-induced AKI is characterized by microvascular dysfunction, inflammation and cellular responses to inflammatory injury (111). The excessive release of inflammatory mediators during sepsis severely disrupts the renal microenvironment (112,113). The pathophysiology of AKI in sepsis is complex and multifactorial, encompassing intrarenal hemodynamic changes, endothelial dysfunction, infiltration of inflammatory cells within the renal parenchyma, and obstruction of renal tubules by necrotic cells and debris (112,113). Furthermore, inflammatory mediators can induce the release of tissue factors and activate the extrinsic coagulation pathway, leading to the formation of microthrombi in the renal microcirculation (98). Ischemia and hypoxia contribute to an increase in ROS within renal tissue, resulting in increased mitochondrial permeability, a decrease in the mitochondrial membrane potential, mitochondrial dysfunction and exacerbation of renal injury (98).

Studies have demonstrated that GLP-1RAs exert renal protective effects through various mechanisms (114-117). For instance, Xiang *et al* (114) demonstrated that early GLP-1 treatment after severe trauma preserved renal function in obese Zucker rats. The authors found that GLP-1 treatment reduced IL-6 levels post-trauma, while maintaining normal renal blood flow, glomerular filtration rate and oxygenation (114). Elkhoely (115) indicated that liraglutide could exert renal protection effects by alleviating oxidative stress, inflammation and apoptosis. This effect was mediated by the upregulation of PKA/CREB signaling and the downregulation of the Notch/Hes-1 pathway, leading to enhanced peroxisome proliferator-activated receptor γ coactivator 1α expression, thus improving gentamicin-induced renal injury in rats (115). Xu *et al* (116) found that liraglutide could mitigate cisplatin-induced nephrotoxicity by inhibiting nuclear-cytoplasmic translocation and release of high mobility group box 1 (HMGB1), reducing inflammatory cytokine levels and HMGB1 receptor expression. Additionally, Li *et al* (117) demonstrated that GLP-1R activation inhibited the TGF-β1/Smad3 and ERK1/2 signaling pathways, preventing epithelial-to-mesenchymal transition, thus reducing extracellular matrix secretion and deposition, and alleviating renal fibrosis. These studies collectively suggest that GLP-1 serves a protective role in kidney injury.

GLP-1RAs and sepsis-related liver dysfunction. During sepsis, systemic inflammatory responses, dysregulated immune responses, hepatic microcirculatory dysfunction and cellular hypoxia can lead to various forms of acute liver dysfunction, including hypoxic hepatitis, sepsis-associated cholestasis or acute liver failure (118). The liver acts both as a mediator and regulator of the immune response, characterized by an increase in acute phase proteins and inflammatory cytokine production. Simultaneously, the liver itself becomes a target organ for injury in sepsis. In sepsis, Kupffer cells, the resident macrophages in the liver sinusoids, become activated and continue to synthesize pro-inflammatory factors (such as TNF-α, IL-6, IL-18 and IL-1β), secrete chemokines and leukotrienes, and initiate ROS and NO production. The locally released pro-inflammatory factors induce inflammatory responses in the liver sinusoids, activating pro-apoptotic signaling cascades (118-120). Additionally, neutrophils, natural killer T cells and sinusoidal endothelial cells contribute to the development of sepsis-related liver dysfunction, ultimately leading to the destruction of hepatocytes and the liver biliary system (118-120).

Overall, the inflammatory cascade is the primary cause of liver injury induced by sepsis (118-120). Studies have shown that liraglutide exerts protective effects during acute liver injury (121,122). Specifically, liraglutide reduced lipid peroxidation (LPO) levels, increased reduced glutathione levels and enhanced SOD activity in a mouse model of acute liver injury, thereby reducing oxidative stress (121). Additionally, liraglutide inhibited carbon tetrachloride-induced hepatic lipid accumulation, promoted hepatocyte proliferation and suppressed apoptosis in the liver, enhancing mitochondrial respiratory function and ultimately providing liver protection effects (121,122). Abdelaziz *et al* (123) demonstrated that liraglutide reduced hepatic enzyme activity, oxidative stress, NF-κB expression and related inflammatory markers, while increasing the expression of the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and downstream phosphorylated CREB, thereby enhancing Nrf2 activity. Furthermore, liraglutide pretreatment resulted

in decreased expression/activity of caspase-3 and a lower BAX/Bcl-2 ratio (123). Similarly, Zhu *et al* (124) suggested that liraglutide exerted liver protective effects by modulating the expression of Nrf2 and antioxidant enzymes in hepatocytes. Additionally, Atef *et al* (62) proposed that the protective effects of liraglutide against hepatotoxicity occur through the improvement of oxidative stress, inflammation and necrotic apoptosis.

GLP-1RAs and sepsis-related gastrointestinal barrier dysfunction. Sepsis alters the intestinal microenvironment, promoting epithelial cell barrier disruption, inflammation and bacterial translocation, leading to enteric infections. The intestine is regarded as a key player in sepsis; damage to the intestinal barrier can result in the entry of numerous bacteria and toxins into the systemic circulation, thereby perpetuating the sepsis-induced inflammatory response (125-127). During sepsis, excessive inflammatory responses and oxidative stress cause microvascular thrombosis, neutrophil-endothelial adhesion and tissue perfusion deficits, resulting in varying degrees of gastrointestinal injury (125-127). GLP-1 can suppress inflammation and promote mucosal integrity. It has been identified as an early biomarker of intestinal mucosal injury. In lipopolysaccharide (LPS)-induced intestinal injury mouse models, the intestine rapidly responds to ischemic damage, characterized by increased GLP-1 secretion following intestinal barrier injury (56). This highlights the importance of GLP-1 in the response to injury and inflammation (56). Furthermore, exogenous GLP-1 can protect the intestine from oxidative damage by inhibiting neutrophil infiltration, and can reduce inflammatory mediators that induce LPO production, regulate intestinal homeostasis through local effects and restore intestinal integrity, thereby reducing bacterial translocation caused by intestinal barrier dysfunction (128).

GLP-1RAs and sepsis-related coagulation disorders. Coagulation dysfunction is prevalent during sepsis, with the pathogenesis primarily involving the release of numerous inflammatory mediators, endothelial cell injury, activation of the extrinsic coagulation pathway, and suppression of anticoagulant and fibrinolytic systems (129). Endothelium, the single-cell layer lining blood vessels, serves a crucial role in various vascular processes, including vascular homeostasis, smooth muscle cell proliferation and thrombus formation/lysis balance (130). GLP-1RAs exhibit protective effects on vascular endothelium (131). *In vitro*, a study has shown that liraglutide reduced the expression of plasminogen activator inhibitor type 1 and vascular adhesion molecules in human vascular endothelial cells, while increasing endothelial NO synthase (eNOS) levels in endothelial cells and reducing the expression of intercellular adhesion molecule-1, thereby improving endothelial function (131). Liraglutide exerts antioxidant and anti-inflammatory effects on endothelial cells by inhibiting protein kinase C-α, NADPH oxidase and NF-κB signaling, while upregulating protective antioxidant enzymes (132). GLP-1RAs have been shown to enhance endothelial function by modulating the expression of genes involved in endothelial apoptosis, angiogenesis, inflammation and thrombosis, specifically by upregulating eNOS and promoting the expression of angiogenesis-related genes, as observed for Ex-4 (133). Steven *et al* (134) found that GLP-1RAs activated GLP-1Rs in platelets via a cAMP/PKA-dependent mechanism, mitigating endotoxemia-induced microvascular thrombosis and mortality, thereby preventing systemic inflammation, vascular dysfunction and end-organ damage.

5. Potential mechanisms of GLP-1RAs in treating sarcopenia induced by sepsis

As aforementioned, during critical illnesses such as sepsis, the body is in a state of oxidative stress, where factors such as excessive release of inflammatory cytokines, mitochondrial dysfunction, dysregulation of calcium homeostasis, neuropathy and abnormal cell membrane depolarization collectively contribute to muscle protein imbalance. Therefore, the present review, starting from the etiology of SIM, explored the potential therapeutic mechanism of GLP-1RAs in SIM. These mechanisms include inhibition of the expression of factors related to muscular atrophy, anti-inflammatory and antioxidant effects, neuroprotection, improvement of metabolism, and promotion of angiogenesis and myogenic differentiation (Fig. 3).

Inhibition of muscle atrophy-related factor expression. The E3 ubiquitin ligases MuRF1 and MAFbx/atrogin-1 serve key roles in skeletal muscle degradation (70). The former induces muscle atrophy by hydrolyzing myosin within myofibrils, while the latter may inhibit protein synthesis by downregulating the expression of eIF3f and MyoD, leading to muscle atrophy (71,72). Gurjar *et al* (135) revealed that long-acting GLP-1 analogs regulated the expression of myostatin through GLP-1R-mediated PKA and Akt signaling pathways, increasing the expression of the myogenic regulatory factors, MyoD and MyoG, while inhibiting the expression of muscle atrophy-related factors MAFbx and MuRF1, thereby promoting muscle tissue growth and repair, and alleviating muscle atrophy. The activated Akt signaling pathway activates downstream mTOR via the Akt-mTOR axis to promote protein synthesis, while also inhibiting NF-κB and the binding of myostatin promoter, reducing myostatin expression to mitigate muscle atrophy (136-138). Myostatin, a member of the TGF-β family, is expressed and secreted in skeletal muscle cells, functioning as a negative regulator of muscle growth. Its gene expression can be inhibited to induce an increase in muscle mass (139). Myostatin primarily mediates the upregulation of MAFbx gene expression through the transcription factors Smad2/3, thereby promoting protein degradation (140,141). Inhibition of the myostatin-Smad2/3 signaling pathway not only alleviates inhibition of the IGF-1-PI3K-Akt-mTOR signaling pathway but also downregulates MAFbx expression (140,141). Hong *et al* (136) found that Ex-4 improved muscle atrophy by inhibiting the expression of myostatin and muscle atrophy factors, while enhancing muscle growth factors through the GLP-1R-mediated signaling pathway. GLP-1RAs can downregulate the expression of the myostatin gene in C2C12 myotubes, reversing the upregulation of atrophy factors and downregulation of myogenic factors (MyoD/G) (136). Silveira *et al* (142) reported that activated cAMP/PKA signaling inhibited the UPS in skeletal muscle, while activated Akt signaling induced protein synthesis in skeletal muscle. On one hand, GLP-1RAs increase the expression levels of MyoD

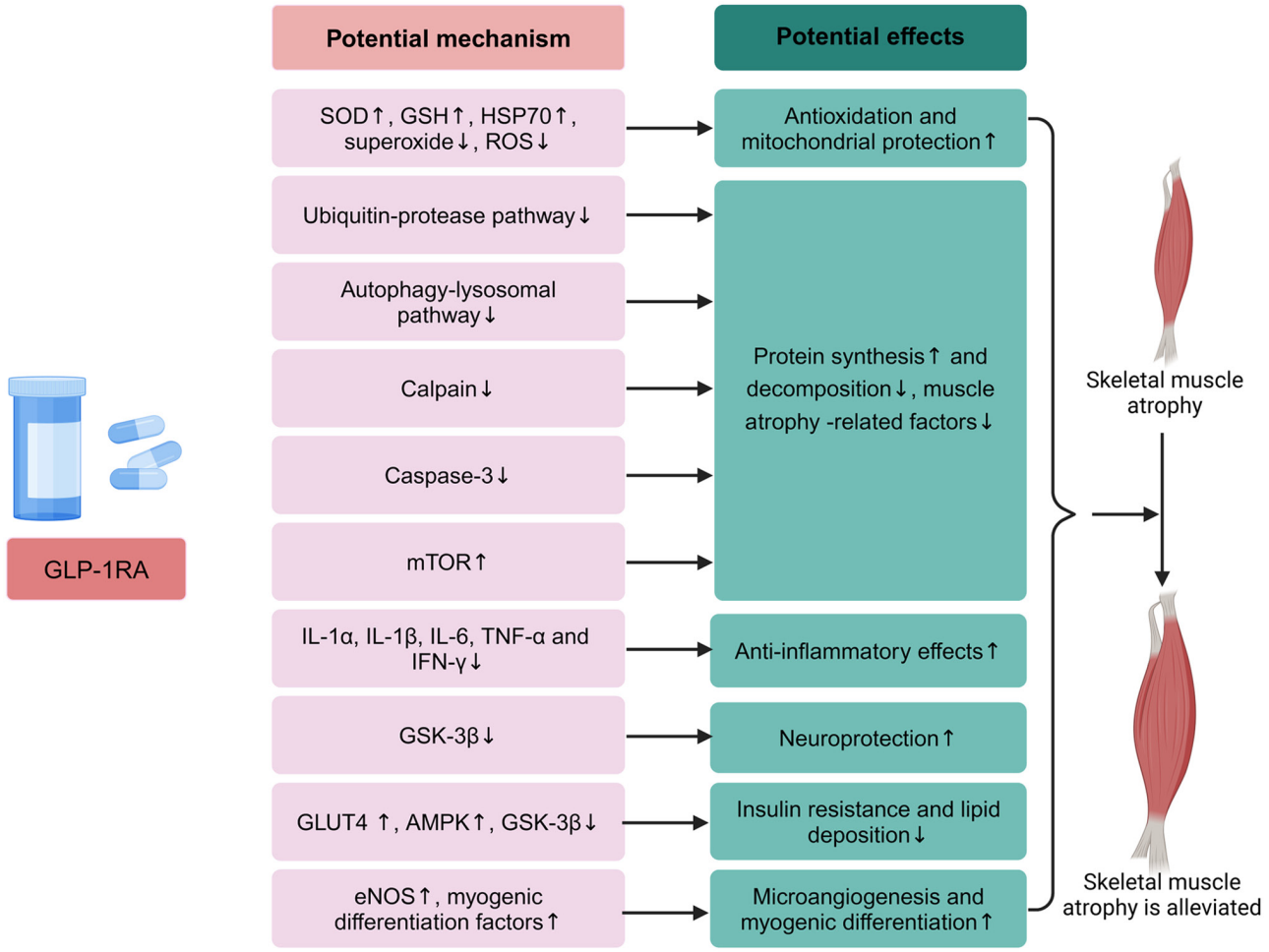

Figure 3. Potential mechanisms of GLP-1RAs in treating SIM. The figure comprehensively shows the potential mechanisms and effects of GLP-1RAs in the treatment of SIM. AMPK, AMP-activated protein kinase; eNOS, endothelial nitric oxide synthase; GLP-1RAs, glucagon-like peptide-1 receptor agonists; GLUT4, glucose transporter 4; GSH, glutathione; HSP70, heat shock protein 70; SIM, sepsis-induced myopathy; ROS, reactive oxygen species; SOD, superoxide dismutase.

and MyoG, which are major transcription factors involved in satellite cell muscle tissue repair (143); on the other hand, PKA-mediated CREB is activated by muscle injury and promotes muscle regeneration (144). Fan *et al* (145) found that liraglutide treatment reduced body weight in diabetic mice and improved the condition of skeletal muscle, accompanied by decreased expression levels of MuRF1 and MAFbx in skeletal muscle.

Anti-inflammatory effects. During sepsis, excessive activation of inflammatory factors leads to protein imbalance, ultimately resulting in increased protein degradation and reduced synthesis, which causes SIM. Therefore, anti-inflammatory interventions can effectively alleviate the onset of SIM (65-68). The NF-κB and Nrf2 pathways are two important pathways that mediate cellular homeostasis by controlling neuroinflammation, while the MAPK pathway is a classical pathway that can indirectly or directly initiate the production of inflammatory mediators and activation of NF-κB (146). Ma *et al* (147) revealed that GLP-1RAs reduced the serum levels of TNF-α, IL-1β and IL-6 in the sciatic nerve of rats, and inhibited the mRNA expression levels of pro-inflammatory cytokines. The anti-inflammatory effect of GLP-1RAs may be mediated through the inhibition of p38 MAPK/NF-κB pathway activation, as activated p38 MAPK/NF-κB promotes the gene expression of TNF-α, IL-6 and IL-1β (147). The study suggests that the p38 MAPK/NF-κB pathway could provide targeted therapeutic approaches for preventing inflammatory changes in diabetic peripheral neuropathy (147). GLP-1RAs inhibit TNF-α-induced NF-κB activation and reduce the expression of adhesion molecules, thereby inhibiting the adhesion of monocytes induced by TNF-α and LPS, exerting anti-inflammatory effects, while reducing vascular endothelial damage (148). GLP-1Rs are expressed on eosinophils and neutrophils, and GLP-1RAs can attenuate eosinophil activation and LPS-induced expression of pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, TNF-α and IFN-γ (23,149,150). Steven *et al* (134) demonstrated that GLP-1RAs activated GLP-1Rs on platelets via the AMP/PKA pathway, inhibiting sepsis-induced microvascular thrombosis, serving an important role in preventing systemic inflammation and vascular dysfunction, and protecting against organ injury.

Mitochondrial protection and antioxidant effects. During sepsis, the body is in a state of stress, with elevated blood glucose levels and increased ROS levels (88,89,151). Notably,

the treatment of animals with mitochondrial antioxidants was able to effectively protect the diaphragm from muscle fiber atrophy and contractile dysfunction induced by mechanical ventilation, further confirming the critical role of ROS in mediating muscle atrophy (151). The production of ROS exacerbates muscle atrophy, as ROS can activate the AMP-activated protein kinase (AMPK)-FoxO3 pathway, leading to the activation of the UPS and lysosomal-autophagy system (152). GLP-1RA treatment increases serum antioxidant enzymes (such as SOD and glutathione), and reduces circulating oxidized low-density lipoprotein particles and oxidative stress markers (153,154). In cardiomyocytes, GLP-1RAs improve mitochondrial fragmentation, while restoring mitochondrial morphology and function in diabetes (153,154). Additionally, it has been reported that GLP-1RAs reduced cardiac oxidative stress in hypertensive mice by lowering ROS levels in whole blood, superoxide and hydrogen peroxide levels in the heart, and 3-nitrotyrosine-positive proteins in the heart (155). Timper *et al* (156) demonstrated that GLP-1R signaling was essential for maintaining mitochondrial integrity and function in astrocytes; a lack of GLP-1R signaling in hypothalamic astrocytes mildly impaired mitochondrial function and induced cellular stress responses.

The glucocorticoid pathway is another signaling cascade involved in proteolysis, activating two major proteolytic cascades: Caspase-3 and the UPS (157,158). Furthermore, glucocorticoids enhance myostatin expression, thereby negatively impacting skeletal muscle (69,158). Research indicates that Ex-4 can upregulate the expression of the glucocorticoid receptor (GR) inhibitory complex, promoting its binding with the GR, which reduces the binding of glucocorticoids to GR and their transport into the nucleus, thereby diminishing the negative effects of glucocorticoids on skeletal muscle (136). On the other hand, heat shock protein 70 (HSP70) is part of the GR inhibitory complex, which can alleviate oxidative stress and act as an anti-inflammatory agent in pro-inflammatory environments by inhibiting the activation of NF-κB, thus counteracting muscle atrophy (159-161). Senf *et al* (162) found that the upregulation of HSP70 could inhibit the expression of muscle atrophy-related factors MAFbx and MuRF1, while also suppressing the transcriptional activity of atrophy-related factors controlled by FoxO and NF-κB genes.

Neuroprotection. One of the causes of muscle atrophy is the dysfunction of the nervous system, leading to denervation atrophy of muscles (13,93). Sadek *et al* (163) demonstrated that GLP-1RAs could activate the bifurcated PI3K/Akt/GSK-3β pathway, which affects cellular function on multiple levels. On the one hand, it improved pathological states associated with neurodegeneration, oxidative stress and neuroinflammation by promoting the phosphorylation of GSK-3β, resulting in its inactivation. On the other hand, GLP-1RA could also increase the level of Nrf2, activate antioxidant and anti-inflammatory mechanisms in the body, and serve an important neuroprotective role (163). In the process of denervation, muscle proteins associated with proteolysis, including atrogin-1/MAFbx and MuRF1, are increased, while expression of proteins associated with protein synthesis, including AKT/mTOR, decreases (70,137,164). Therefore, GLP-1RAs may promote protein synthesis and alleviate denervation atrophy by activating the IGF-1-PI3K-Akt-mTOR signaling pathway (70,137,164). Additionally, Mohiuddin *et al* (165) indicated that GLP-1RAs exerted neuroprotective effects through direct action on root ganglion neurons.

Improvement of insulin resistance and reduction of lipid accumulation in skeletal muscle. Systemic insulin resistance often accompanies trauma or severe illness (166). As aforementioned, GLP-1RAs can improve insulin resistance and promote insulin secretion. Semaglutide, a type of GLP-1RA, was found by Sadek *et al* (163) to inhibit GSK-3β activity through the PI3K/Akt/GSK-3β pathway, promoting glycogen synthesis in muscle. Glucose transporter 4 (GLUT4) is an insulin-dependent glycoprotein that is expressed in muscle, fat and bone, and its expression and displacement affect glucose uptake in muscle and adipose tissue (167). Research shows that exenatide and liraglutide can activate the AMPK pathway, promoting GLUT4 translocation in an insulin-independent manner, thus increasing glucose uptake in skeletal muscle (168). A study has indicated that high glucose levels activated JNK and p38 MAPK after 12 weeks without causing cell damage. However, oxidative stress activated ERK and p38 MAPK after 8 weeks, leading to cell damage (169). p38 MAPK can activate chromatin remodeling proteins and myogenic transcription factors, serving an important role in muscle differentiation (170). Additionally, in rat cardiomyocytes, the p38 MAPK/myocyte enhancer factor 2 axis is a strong inducer of GLUT4 expression (171). However, liraglutide inhibits the p38-MAPK/NF-κB pathway (147). Therefore, we hypothesized that p38 MAPK may enhance skeletal muscle mass by regulating myocyte differentiation and promoting glucose uptake, improving the energy metabolism of skeletal muscle. On the other hand, GLP-1RAs can inhibit the excessively activated p38 MAPK/NF-κB pathway, exerting antioxidant effects (147).

Excessive lipid accumulation in skeletal muscle cells, and the free fatty acids produced from their breakdown, inhibit glucose utilization in skeletal muscle (172). AMPK also serves a role in regulating lipid and protein metabolism by inhibiting the generation of transcription factors that bind to sterol regulatory elements, suppressing the synthesis of lipid biosynthetic enzymes in tissues, inhibiting fat synthesis, increasing fatty acid oxidation and reducing lipid accumulation (173). Cao *et al* (174) demonstrated that Ex-4 reduced lipid accumulation and insulin resistance in the skeletal muscle of obese mice induced by a high-fat diet by activating AMPK and upregulating insulin signaling pathways.

Recruitment of skeletal muscle microvasculature and induction of myogenic differentiation. GLP-1RAs can increase microvascular perfusion in skeletal muscle through various pathways (175-178). For example, as aforementioned, GLP-1RAs are present in vascular endothelial cells. GLP-1 analogs can increase microvascular perfusion in skeletal muscle through the PKA-NO pathway, and they can also enhance microvascular perfusion independently of NO (175). Furthermore, GLP-1RAs improve insulin resistance. Insulin, by binding to its receptor, activates the PI3K-Akt-eNOS pathway to produce NO, mediating vasodilation (176). Improved microcirculation in skeletal muscle aids in the

delivery and exchange of oxygen, nutrients and insulin, thus nourishing muscle tissue (176). Subaran *et al* (177) indicated that acute GLP-1 infusion not only dilated blood vessels but also recruited skeletal and cardiac microvascular systems. Chai *et al* (178) demonstrated that GLP-1 infusion increased PKA activity, promoting the phosphorylation of eNOS, subsequently increasing plasma NO levels, enhancing muscle oxygenation and glucose uptake, and recruiting the microvascular system via NO-dependent mechanisms, which increased glucose utilization in muscles. Gurjar *et al* (135) also reported that liraglutide could induce C2C12 myoblast differentiation through cAMP-dependent signaling events, promoting myogenesis and alleviating muscle atrophy. *In vitro* experiments demonstrated that GLP-1RAs promoted myogenic differentiation in a dose-dependent manner, while concurrently reducing the transcriptional expression of MAFbx and MuRF1 in myoblasts in a dose-dependent manner (145). A further *in vitro* study on myogenic differentiation confirmed that liraglutide could promote myogenic differentiation, alleviate myotube atrophy, and inhibit the upregulation of atrophy-induced MAFbx and MuRF1 mRNA expression, ultimately contributing to the preservation of muscle mass (145).

6. Clinical safety and limitations

GLP-1RAs are commonly used medications for diabetes treatment and have gained attention due to their weight loss effects (19-21). Studies have shown that the regulatory effects of GLP-1RAs on metabolism and inflammatory responses may offer potential benefits for sepsis and associated muscle atrophy (23,59-64). However, there are still certain limitations when using GLP-1RAs to treat SIM. Relevant reviews have reported serious adverse events associated with GLP-1RAs, among which gastrointestinal diseases (commonly nausea, diarrhea, vomiting and constipation) are the most frequently reported; however, most gastrointestinal events are of mild to moderate severity, transient and do not require permanent discontinuation of treatment (179,180). Other reported adverse reactions include allergic reactions, cardiovascular, psychiatric and thyroid-related events, as well as biliary diseases and pancreatitis (179,180). Additionally, small sample sizes, short durations and selective participant recruitment limit the identification of rare or long-term adverse events. Tobaiqy (179) noted that clinicians must weigh the risks and benefits, monitor patients for adverse events, and conduct ongoing long-term safety assessments, especially regarding the cumulative effects and susceptibilities in specific populations. Although numerous studies (135,145) suggest that GLP-1RAs may have protective effects against sepsis and sepsis-induced muscle atrophy, most studies (135,145) primarily focus on animal models, with limited clinical research available. Currently, to the best of our knowledge, there are no clinical reports of GLP-1RA treatment for SIM, and the long-term efficacy and safety in patients with SIM have not been sufficiently validated. For instance, some studies have found that GLP-1RAs can cause or exacerbate muscle atrophy, leading to a decrease in muscle mass, this contradicts the hypothesis that GLP-1RAs have therapeutic potential in SIM (181,182). Therefore, further verification of the long-term efficacy and safety in clinical settings is necessary. Additionally, sepsis is a systemic inflammatory response syndrome induced by infection, often accompanied by multiple organ system failures (1). The mechanisms of muscle atrophy in sepsis are complex and not yet fully elucidated (69). Due to the multifactorial and complex nature of sepsis-induced muscle atrophy, treatment typically requires multidisciplinary approaches. Patients with sepsis often have multiple comorbidities, such as diabetes and hepatic or renal insufficiency. These factors can affect the pharmacokinetics and pharmacodynamics of GLP-1Ras (1). Thus, in some cases, GLP-1RAs may not be suitable for certain patients. Currently, there are no effective treatments for SIM, with a focus on prevention, commonly involving blood glucose control, early anti-inflammation treatment, early enteral nutrition, and early exercise and rehabilitation (13). Therefore, GLP-1RA treatment alone may not address all relevant mechanisms and is more likely to serve as an adjunct therapy. Recent reviews indicate that mesenchymal stem cells and melatonin hold certain potential in the treatment of sepsis-related muscle atrophy (10,98). Consequently, if GLP-1RAs are used in the treatment of sepsis-related muscle atrophy, they may need to be combined with other medications.

7. Outlook and conclusion

Sepsis is a systemic inflammatory response syndrome caused by infection, characterized by organ dysfunction and metabolic imbalance, and often accompanied by muscle atrophy. Muscle atrophy is common in patients with sepsis, leading to prolonged recovery times, reduced quality of life and even an increased risk of mortality. Currently, there are no specific therapies available for SIM, a situation that may be attributed to several factors. On the one hand, the pathophysiological mechanisms underlying SIM are complex, involving processes such as inflammation, oxidative stress and metabolic dysregulation, which pose challenges to the development of targeted treatments. On the other hand, SIM typically occurs in critically ill patients with sepsis or other systemic diseases, potentially limiting the feasibility of conducting large-scale clinical trials. Nutritional support and rehabilitation training are generally regarded as supportive rather than curative interventions. The primary goal of nutritional support is to alleviate malnutrition and promote muscle protein synthesis, while rehabilitation training aims to preserve muscle function and prevent further atrophy. However, these approaches have shown limited efficacy in reversing SIM, as they do not directly address the underlying mechanisms driving muscle atrophy. This underscores the urgent need for the development of novel therapeutic strategies.

GLP-1RAs have emerged as a potential therapeutic approach. Although clinical research on GLP-1RAs in SIM is still limited, some preliminary evidence (135,145) supports the improvement of muscle mass and function by GLP-1 analogs. Additionally, GLP-1RAs exhibit organ-protective effects on the heart, brain, kidneys, lungs, liver, intestines and vasculature in the context of septic multi-organ dysfunction. However, there is currently a lack of focused reviews on the relationship between GLP-1RAs and sepsis-related muscle atrophy. The

present review may help fill the existing gaps in the literature and provide directions for future research.

Numerous studies (135-178) have indicated that GLP-1RAs can reduce oxidative stress, inflammatory responses, apoptosis and mitochondrial dysfunction, improve insulin resistance, and induce myogenic differentiation, thereby showing potential in the treatment of SIM. Consequently, the present review discusses the possibilities of GLP-1RA therapy for SIM in detail and elaborates on its potential therapeutic mechanisms. Although GLP-1RAs exhibit certain potential in some metabolic and inflammatory diseases, their use as a treatment option for sepsis-induced muscle atrophy still faces numerous limitations, particularly concerning insufficient clinical evidence, complex therapeutic mechanisms, drug side effects and individual variability. Therefore, the application of GLP-1RAs in sepsis-related muscle atrophy requires more clinical research and practice to validate their efficacy and safety, and GLP-1RAs may need to be combined with other therapeutic approaches to achieve maximum effectiveness.

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Availability of data and materials

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Authors' contributions

XZ, YL, DW, TL, ZX, ZL, XB and YW contributed to the design of the study and writing of the manuscript. XZ, YL, DW, TL and ZX performed the literature research. XZ and YW wrote the main manuscript text and prepared figures. ZL, XB and YW revised the article critically for important intellectual content and provided final approval of the version to be submitted. All authors reviewed the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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